STUDIES ON THE GENERATION AND USE OF FUNCTIONALISED ORGANOZINC CARBENOIDS FOR THE SYNTHESIS OF AMINOCYCLOPROPANES AND RELATED CONGENERS

A Thesis Presented by

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ABSTRACT

The present thesis describes a range of studies on the generation and reactivity of organozinc carbenoid species possessing adjacent nitrogen functionality for the preparation of aminocyclopropanes and related congeners.

This thesis opens with two distinct introductory reviews. The first one focuses on the description of the different general methods already available for the synthesis of aminocyclopropanes. The second one is concerned with the generation and reactivity of organozinc carbenoids encountered in the literature.

The results and discussion chapter firstly describes the successful generation of an organozinc carbenoid from an acetal moiety contiguous to a nitrogen atom of a simple cyclic amide using a mixture of zinc amalgam and chlorotrimethylsilane. This new organometallic species is found to undergo cyclopropanation reactions with a range of alkenes to yield amidocyclopropanes.

Subsequent studies directed towards the design of carbenoid precursors which can lead to the preparation of primary aminocyclopropanes are then discussed. A method for the synthesis of chiral protected aminocyclopropanes in two steps from their corresponding alkenes is described.

An investigation of the preparation of *N*-substituted cyclopropyl amino alcohols and acids is presented. From this study, an *N*-substituted cyclopropyl glycine derivative is prepared.

Finally, this thesis discusses the attempted palladium-catalysed cross-coupling reactions between amino cyclopropylsilanes and aryl iodides and the successful Tamao-Fleming oxidation of the carbon-silicon bond of vicinal amino cyclopropylsilanols to give the corresponding amino cyclopropanols.

The thesis terminates with a full description of the experimental procedures used and the compounds prepared.

DECLARATION

The research described in this thesis is, to the best of my knowledge, original except where due reference is made to other authors.

CONTENTS

ACKNOWLEDGEMENTS

I would firstly like to thank my supervisor, Professor Willie Motherwell, for his guidance, help and encouragements over the past three years. I am also very grateful to my industrial supervisor at AstraZeneca, Doctor David Cladingboel, for his advice, enthusiasm and having arranged my very enjoyable three-month industrial placement in Loughborough.

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Most of all I would like to thank my parents, Dominique and Marie-Christine, for their constant support and help, and Mina-chan for her encouragements during my PhD, having left her so loved Japan to join me in Europe and all the happiness that she is bringing to me.

ABBREVIATIONS

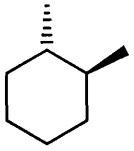
Ac	acetyl
All	allyl
Ar	unspecified aryl group
arom	aromatic
BINAP	2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
Boc	*tert*-butoxycarbonyl
Bu	butyl
Bn	benzyl
br	broad
c	cyclo
cat.	catalytic
CI	chemical ionisation
Δ	reflux
dba	dibenzylideneacetone
DCE	dichloroethane
DMF	*N,N*-dimethylformamide
DMS	dimethylsulfide
DMSO	dimethyl sulfoxide
EI	electron impact
ee	enantiomeric excess
eq	molar equivalent(s)
Et	ethyl
FAB	fast atom bombardment
g	gram(s)
GC	gas chromatography
h	hour(s)
Hz	Hertz
i	*iso*
IPA	isopropyl alcohol
J	coupling constant
L	unspecified ligand

LA	Lewis acid
LiHMDS	lithium bis(trimethylsilyl)amide
lit.	literature value
M	unspecified metal
m	medium
m-CPBA	3-chloroperoxybenzoic acid
Me	methyl
min	minutes
mL	millilitre(s)
mp	melting point
n	*neo*
NCS	*N*-chlorosuccinimide
NMR	nuclear magnetic resonance
Nu	nucleophile
p	*para*
ppm	parts per million
Ph	phenyl
Phth	phthalimide
PMP	*para*-methoxyphenyl
Pr	propyl
s	strong
R	unspecified carbon substituent
R_F	retention factor
rt	room temperature
t	*tert*
TBAF	tetrabutylammonium fluoride
TBDMS	*t*-butyldimethylsilyl
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	trimethylsilyl
Ts	*para*-toluenesulfonic
w	weak
wt.	weight
X	leaving group

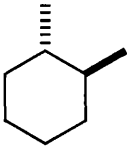
Y	functionalised group

STEREOCHEMICAL NOTATION

Throughout this thesis, the graphical representation of stereochemistry is in accord with the conventions proposed by Maehr.* Thus, solid and broken wedges denote absolute configuration and solid and broken lines denote racemates. For the former, greater narrowing of both solid and broken wedges indicates distance from the viewer.



single enantiomer



racemic

* Maehr, J. *J. Chem. Ed.* **1985**, *62*, 114.

Chapter 1

Introduction

1 Introduction

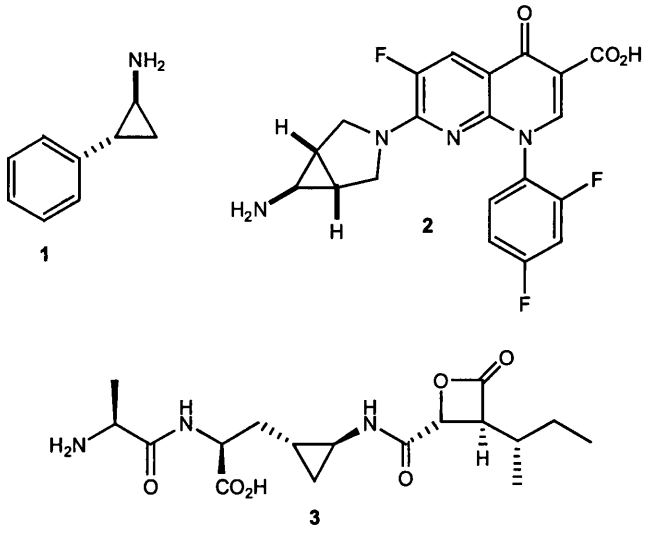
The present thesis is concerned with a study of the generation and reactivity of functionalised organozinc carbenoids and in particular their use for the synthesis of aminocyclopropanes and related congeners.

In order to place this work in perspective, the following introduction is divided into two distinct parts. The first focuses on a description of those methods already available for the preparation of aminocyclopropanes. This account is done with a critical eye, trying to present both the advantages and also the drawbacks of these methods, thereby allowing the reader to compare and estimate the value of our own method which is presented in the following chapter of Results and Discussion.

For a better comprehension of the behaviour of the carbenoid species involved in this work, a presentation of the generation, structure and reactivity of organozinc carbenoids reported in the chemical literature is provided in the second part of this introduction. Emphasis has been given to the chemistry developed in this area within our own group.

1.1 Synthesis of cyclopropylamines

The development of new routes towards the synthesis of cyclopropylamines still represents an exciting challenge for chemists since reported approaches for their preparation generally suffer from a lack of generality and/or efficiency. As aminocyclopropanes have recently received increased attention on account of their diverse biological activities,[1] the emergence of more practical methods for their preparation would be highly valuable. From the numerous natural and non-natural biologically active cyclopropylamines the commercially available antidepressant Tranylcypromine **1**, the broad-spectrum antibacterial Trovafloxacin **2** and the natural product Belactosin A[2] **3** are probably the most significant examples at present (Scheme 1).



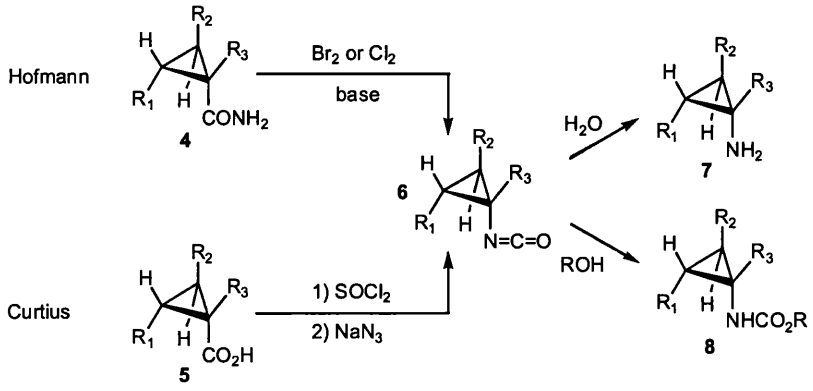
Scheme 1

This introduction will concentrate on describing the different general and reasonably efficient methods which have been employed to prepare cyclopropylamines. Ways to access cyclopropane amino acids, principally 2,3-methanoamino acid derivatives, have been intensively reviewed and will not be included as they usually involve strategies which are not applicable for the synthesis of simple alkyl or aryl aminocyclopropanes.[3,4]

Vilsmaier comprehensively reviewed the chemistry of cyclopropylamines in 1987 but since then, no report covering more recent advances in this field has been published.[5]

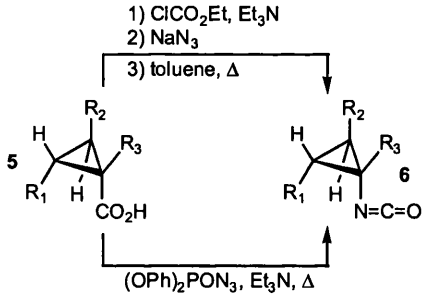
1.1.1 By cyclopropyl migration *via* a Hofmann or Curtius rearrangement

The most common way to prepare aminocyclopropanes relies on classical Hofmann or Curtius degradation of a carboxylic acid derivative of type **4** or **5** (Scheme 2).[5] Both processes involve the generation of an acyl nitrene which rearranges to yield an isocyanate **6**. This latter intermediate can either be hydrolysed to the corresponding amine **7** or be trapped by an alcohol (usually used as the solvent) to yield a carbamate **8**.



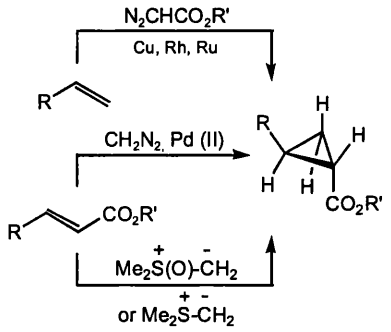
Scheme 2

From the differing modifications of the Curtius rearrangement, the method introduced by Weinstock[6] involving the reaction of a mixed anhydride with sodium azide and that developed by Yamada *et al.*[7] employing the nonexplosive diphenylphosphoryl azide have proven to be the most popular (Scheme 3). It is also important to note that when these conditions are followed, the rearrangement occurs stereospecifically with total retention of both optical and geometrical configuration.



Scheme 3

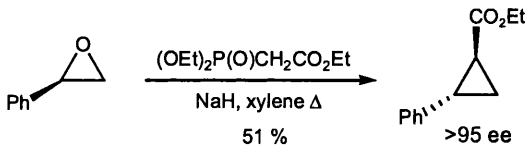
The cyclopropyl carboxylic acid precursors for these transformations are usually derived from saponification of their corresponding esters, and these latter compounds can, in turn, be synthesised in numerous ways (Scheme 4). The most common routes involve metal-catalysed cyclopropanation reaction, either of alkyl diazoacetates with alkenes (usually with Cu and Rh and more recently Ru) or diazomethane with alkyl cinnamates (most commonly with Pd(II)), or the Michael-initiated ring closure reaction of alkyl cinnamates with sulfur ylides.[8]



Scheme 4

Recent developments of these reactions have allowed the preparation of selected cyclopropyl esters with excellent stereo- and/or enantiospecificities. Interested readers are directed towards the referenced reviews.[8]

An alternative method, first developed by Wadsworth and Emmons[9] in 1961 and involving the reaction between an epoxide and a phoshonoacetate enolate, has recently received increased attention.[10] Starting with an enantiomericely pure epoxide, it was demonstrated that this process occurs with almost complete inversion of the epoxide configuration (Scheme 5).



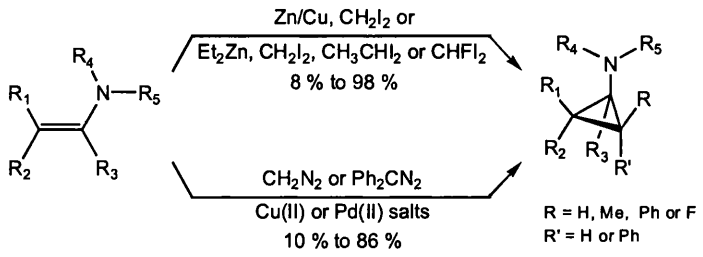
Scheme 5

Although the methods outlined above for the preparation of cyclopropylamines involving a Hofmann or Curtius rearrangement are fairly general, the overall process nevertheless requires a minimum of four steps and rarely achieves more than a 50% overall yield.

1.1.2 By cyclopropanation of enamines and enamides

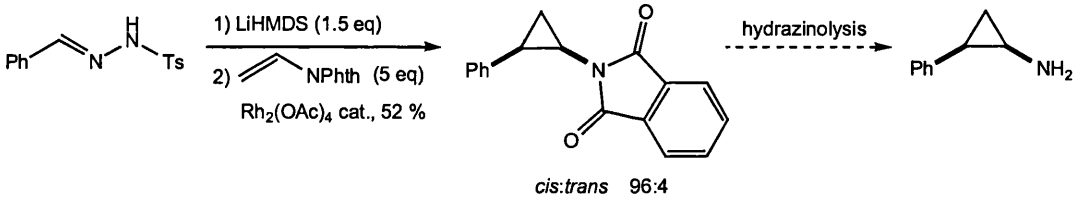
The cyclopropanation of enamines and related congeners appears, in principle, to be a very straightforward route towards the synthesis of aminocyclopropanes. This reaction

is commonly performed either with an organozinc carbenoid,[11,12,13,14] IZnCHRI (R=H, Me or F), or an alkyl diazo compound, such as diazomethane or diphenyldiazomethane, in the presence of a copper (II)[12,15] or palladium (II)[16] salt. The desired products are formed however in very variable yields (Scheme 6).



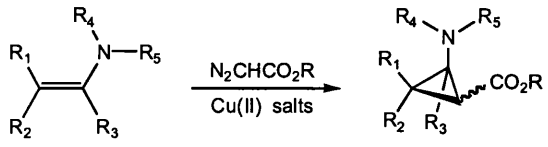
Scheme 6

More recently Aggarwal *et al.* reported a useful practical modification involving *in situ* generation of aryldiazomethanes from hydrazone derivatives, thus avoiding the handling of hazardous diazoalkanes.[17] When applied to the cyclopropanation reaction of *N*-vinylphthalamide this approach appears to be a particularly effective method for preparation of *cis* 2-arylcyclopropylamines (Scheme 7).



Scheme 7

Within the scope and uses of copper-catalysed cyclopropanations, reactions using alkyl diazoacetates with enamines have received increasing attention since the product β-aminocyclopropanecarboxylic acids are interesting building blocks for peptide chemistry (Scheme 8).[3e]

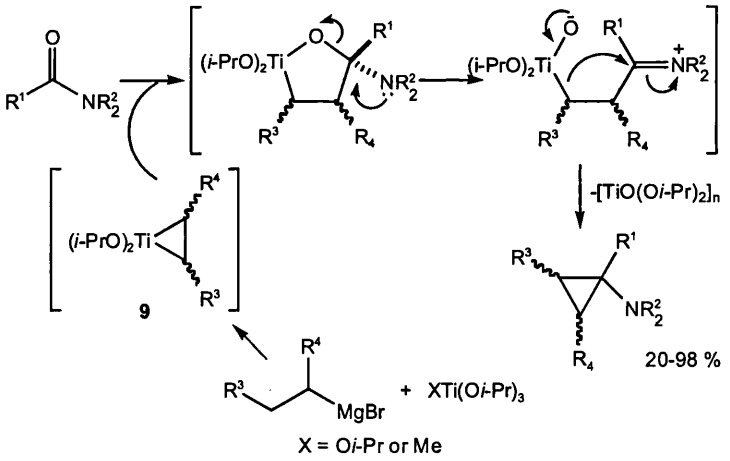


Scheme 8

1.1.3 By titanium-mediated cyclopropanation of carboxamides and nitriles

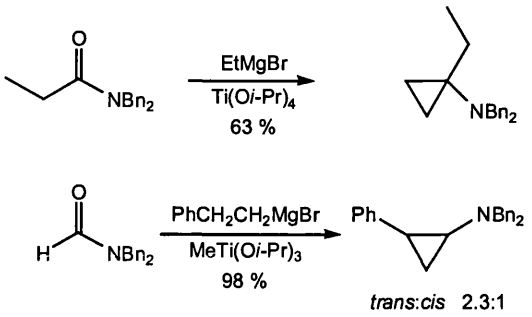
Within the last decade, a new cyclopropanation reaction mediated by titanium species has emerged. Initially developed by Kulinkovich[18] for the preparation of cyclopropanols from esters, this method was then adapted by de Meijere[19] for the synthesis of aminocyclopropanes. In this present introduction only a concise overview of this methodology is given, and more details and tables of results can be found in several reviews which have recently appeared.[20]

In essence, when treated with alkylmagnesium halides, titanium alkoxide derivatives form titanacyclopropane intermediates of type **9**[20] which then act as 1,2-dicarbanionic species and react with *N,N*-dialkylcarboxamides yielding cyclopropylamines (Scheme 9).[19,21]



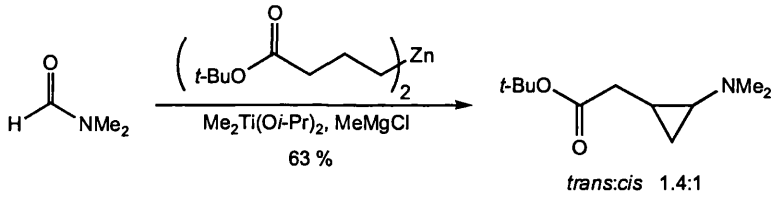
Scheme 9

This reaction has been applied successfully to a range of carboxamides and Grignard reagents and some selected examples are shown in Scheme 10. The use of methyltitanium triisopropoxide instead of titanium tetraisopropoxide was subsequently found to be preferable as yields of cyclopropylamines are generally higher.[21] *N,N*-dibenzylcyclopropylamines can yield primary cyclopropylamines by simple hydrogenolysis. However, this method cannot be applied to all substrates, especially those possessing an aryl group attached to the cyclopropane, since cyclopropyl rings are known to be hydrogenated with ring opening under such conditions.



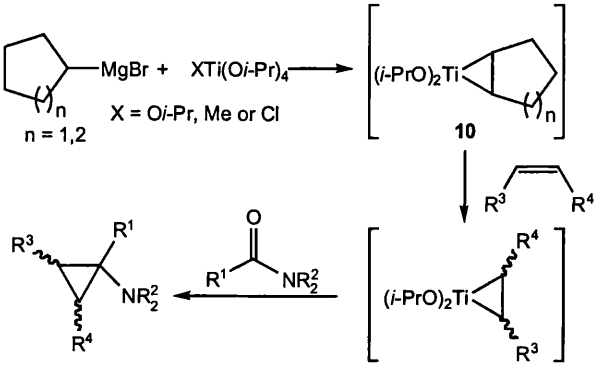
Scheme 10

Applying a somewhat modified protocol allows functionalised organozinc derivatives to be employed (Scheme 11).[22]



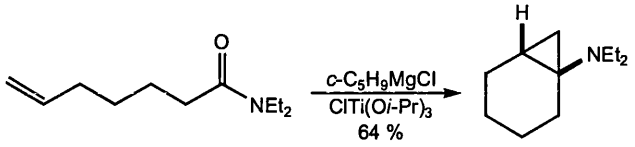
Scheme 11

The general method was then greatly improved when some titanacyclopropane intermediates were found to undergo rapid ligand exchange with added alkenes.[23] Intermediates of type **10**, prepared by the reaction of cyclopentyl[24]- or cyclohexyl[25] magnesium halide appeared to be the best for this purpose. This overall process may be considered as a dialkylaminocyclopropanation of alkenes (Scheme 12).



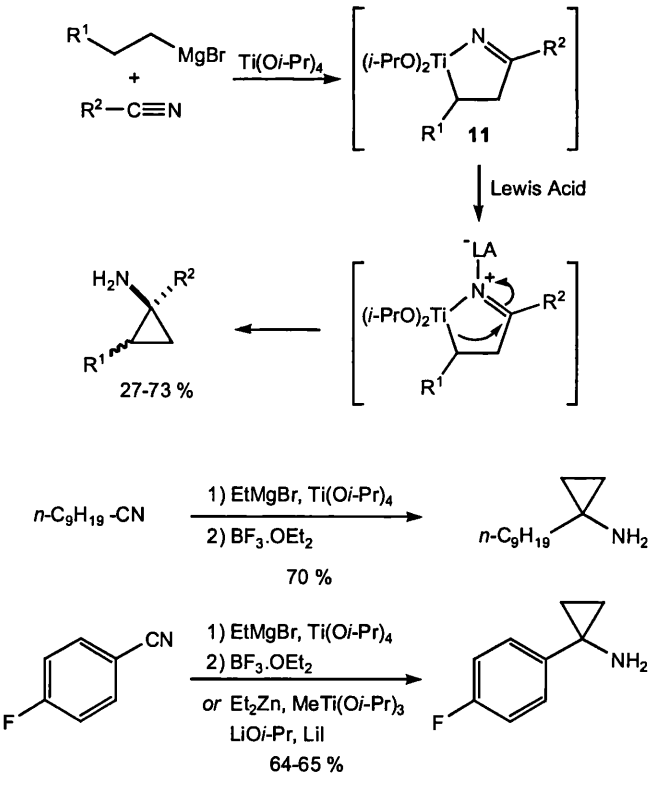
Scheme 12

The intramolecular variant of this reaction has also been developed for terminal alkenes as depicted for the example in Scheme 13.[24]



Scheme 13

More recently aliphatic and aryl nitriles were found to undergo similar reactions yielding primary 1-substituted aminocyclopropanes. In most cases a Lewis acid, such as $BF_3.OEt_2$ or $TiCl_4$, has to be present to initiate the contraction of the azatitanacycle **8** (Scheme 13).[26] A variant using diethyl zinc and methyltitanium triisopropoxide in the presence of lithium salts has also been reported for aryl nitriles and gives comparable results (Scheme 14).[27]

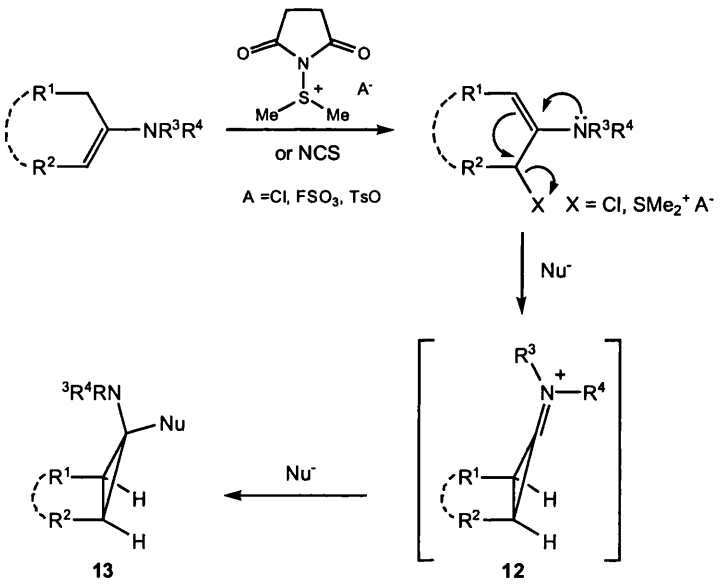


Scheme 14

To date, the titanium-mediated cyclopropanation reaction appears to be the most direct route to prepare aminocyclopropanes. However this new method is usually limited to the preparation of poorly functionalised cyclopropylamines as the use of Grignard reagents is incompatible with a number of functional groups such as carbonyl groups and halogens. In addition, an efficient chiral version of this reaction still remains to be developed.[20b]

1.1.4 Reactions involving 1,3-ring-closure

A widely applicable method for the preparation of substituted bicyclic cyclopropanes has been developed based on 1,3-ring-closure reaction. The description of this approach has received particular attention in the review written by Vilsmaier[5] and then in 1997 in a chapter of "Methods of Organic Chemistry" dedicated to the synthesis of cyclopropanes.[28] The principle of this method is to induce a ring closure reaction by the reaction of a nucleophile with an enamine possessing an adjacent leaving group such as chloride anion or a dimethylsulfonium group (Scheme 15).

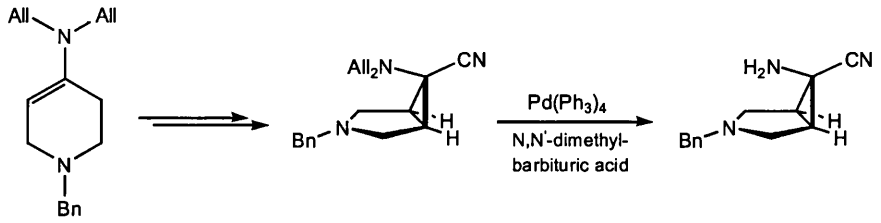


Scheme 15

Generally, *endo* cyclopropylamines **13**, resulting from kinetically preferred attack of nucleophiles at the sterically less hindered face of cyclopropyliminium cation **12** are the

exclusive or predominant products. The reaction has been shown to be very broad in scope as a wide range of nucleophiles can be successfully used.[5,28]

The synthetically utility of this approach has been recently broadened by the preparation of primary aminocyclopropanes starting with enamines having a removable group for R^3 and R^4 (Scheme 15), such as a benzyl or allyl group (Scheme 16).[29]

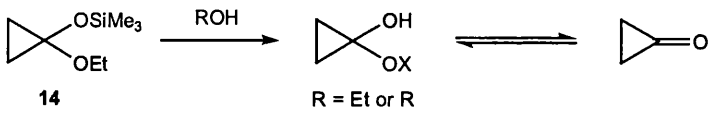


Scheme 16

This methodology generally gives good yields and stereoselectivities of cyclopropylamines starting with 6 or 7 member ring enamines, it appeared that for other ring sizes the results obtained are more variable.[28]

1.1.5 By reaction with a "cyclopropanone equivalent"

An alternative approach for the preparation of cyclopropylamines proceeds *via* a cyclopropanone derivative.[30] As cyclopropanone itself is not a stable compound, [(1-ethoxycyclopropyl)oxy]trimethylsilane **14**, which is commercially available, is the starting material commonly used in this chemistry. This reagent is readily desilylated in alcohol to give a cyclopropanone hemiketal which is in equilibrium with the parent ketone (Scheme 17).

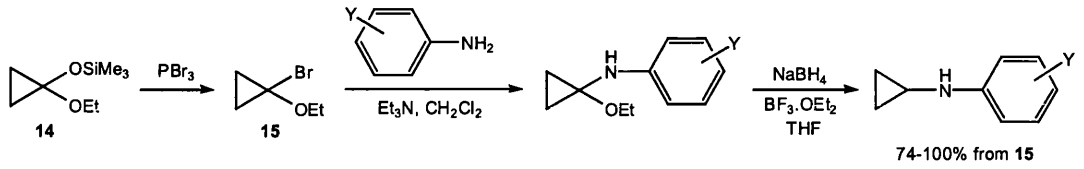


14 R = Et or R

Scheme 17

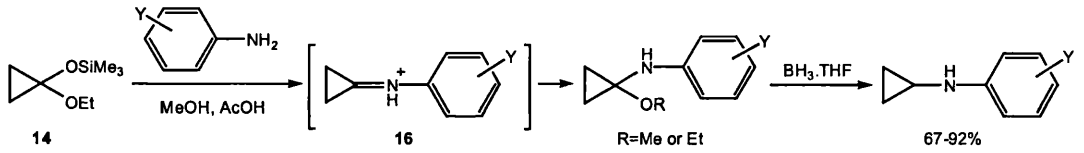
Kang *et al.* have described an *N*-cyclopropylation reaction by the direct substitution of the bromine atom of cyclopropane **15** by an aromatic amine and subsequent reductive dealkoxylation in the presence of sodium borohydride and a Lewis acid (Scheme 18).[31]

The presence of an electron-donating group on the same carbon as the bromine atom is imperative for effective displacement by the nucleophile on such a cyclopropyl ring.[30,32]



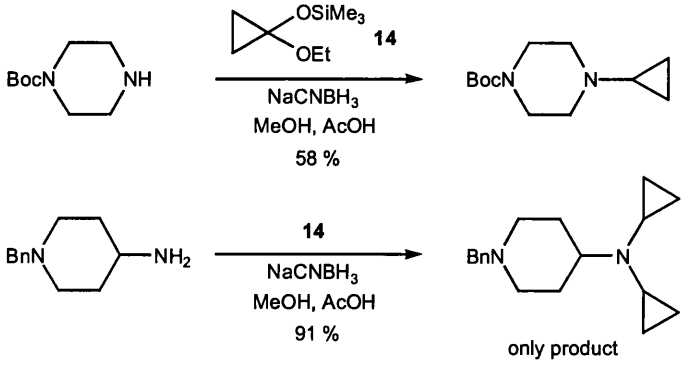
Scheme 18

More recently Yoshida *et al.* have simplified this process by performing the condensation of the aniline directly with **14** in an acidic medium to yield the desired product in two straightforward steps (Scheme 19).[33] The first reaction almost certainly involves the formation of the iminium cation **16** at some stage since most of the ethoxy group of **14** is replaced by the solvent.



Scheme 19

Another method consists of the one-pot reductive amination of aliphatic and aromatic amines with **14**. However mono-cyclopropylation of aliphatic primary amines cannot be achieved following this protocol (Scheme 20).[34]

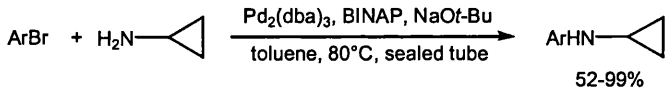


Scheme 20

These methods are complementary to those already presented, but have so far been restricted to the introduction of the simplest cyclopropyl unit since substituted cyclopropanones are not readily available.

1.1.6 Via palladium-catalysed C-N bond formation

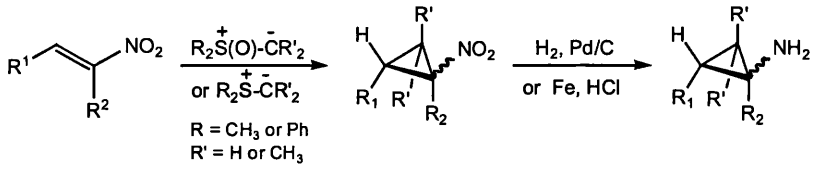
A practical method for the synthesis of *N*-arylcyclopropylamines has recently been developed by Loeppky *et al.*.[35] Their approach is based on the palladium-catalysed amination reaction of aryl bromides with cyclopropylamine. Using the standard conditions for this type of cross-coupling reaction a range of *N*-cyclopropylaromatic amines were prepared in moderate to excellent yields (Scheme 21).[36]



Scheme 21

1.1.7 By reduction of nitrocyclopropanes

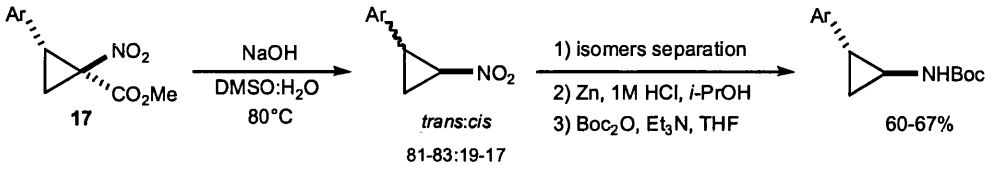
Nitrocyclopropanes can of course be considered as obvious precursors of cyclopropylamines by reduction of the nitro group. Their synthesis is commonly performed by Michael-initiated ring closure reactions of nitroalkenes with sulfur ylides followed by reduction of the nitro group either by catalytic hydrogenation or by reaction with iron in the presence of hydrochloric acid (Scheme 22).[37,38]



Scheme 22

Taking into account the two steps usually required for the preparation of nitroalkenes[39] and the relative instability of this class of compounds, the overall process appears to be tedious and low yielding.

Arylcyclopropylamines can also derived from 1-nitrocyclopropane carboxylates **17** after decarboxylation and subsequent reduction of the nitro function (Scheme 23).[40]

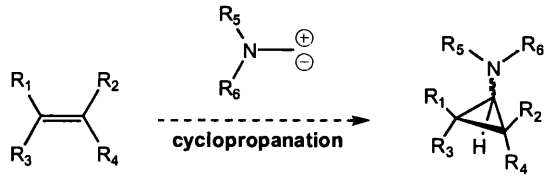


Scheme 23

Compounds of type **17** are conveniently prepared in one step by a rhodium-catalysed cyclopropanation reaction involving either the use of α-nitro- α-diazocarboxylates [40,41,42] or α-nitroesters in the presence of iodobenzene diacetate.[40,42]

1.1.8 By addition of aminocarbenes or carbenoids to alkenes

In conceptual terms, this strategy can be seen as one of the most convergent since the aminocyclopropane derivative is formed in a single step from readily available alkenes as starting materials (Scheme 24).

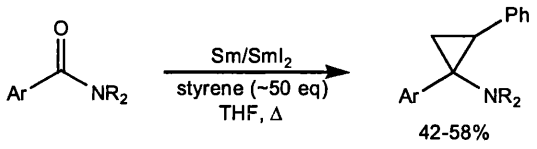


Scheme 24

In practice however, only a few papers, to date, relate the successful use of such aminocarbenes for the cyclopropanation of alkenes and this is usually with limited practical applications.[43,44]

Within the field of carbenoid chemistry, Ogawa *et al.* have shown that, for the specific cases of *N,N*-disubstituted aromatic amides, treatment with a mixture of samarium and samarium diiodide yields an organosamarium carbenoid species which is capable of cyclopropanating styrene (Scheme 25).[45] However this reaction has limited efficiency as

it requires the use of a large excess of alkene and the yields obtained are low to moderate.



Scheme 25

1.1.9 Summary

From the foregoing overview, it is apparent that existing methods for the preparation of various aminocyclopropanes often require multistep sequences and/or are not compatible with a number of functional groups. Moreover, and especially so for those reactions in which formation of the cyclopropane is achieved in two discrete carbon-carbon bond forming steps, stereochemical issues may become complicated.

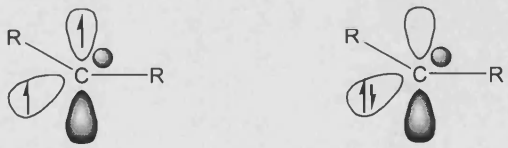
Whilst metal mediated addition of carbenoids to enamine derivatives appears to offer a more direct approach to stereocontrolled aminocyclopropane synthesis, it is however limited in terms of the possible substituents on the carbenoid carbon. As we have seen, the direct addition of a carbenoid bearing useful nitrogen functionality has been reported in only one specific case, involving samarium/samarium diiodide reduction of *N,N* disubstituted aromatic amides. The de Meijere variant of the Kulinkovich reaction, which continued to be studied during the course of our own work, is especially noteworthy in terms of conceptual elegance and practicality.

1.2 Organozinc carbenoids

The second section of this present introduction is concerned with the preparation and reactivity of different organozinc carbenoids encountered in the literature. It will start with a definition of carbenoids and then move to the study of common organozinc carbenoids employed for the cyclopropanation of olefins, such as the Simmons-Smith reagent. The final section will then go on to describe in more detail, the discovery, generation and reactivity of organozinc carbenoids from carbonyl compounds and related congeners. This last part is of particular relevance because of its direct link with the evolution of the work carried out in the present thesis.

1.2.1 Carbenes and carbenoids

Carbenes are generally considered as neutral two-coordinate carbon reactive intermediates with two nonbonding electrons which may have either anti parallel spins (singlet state) or parallel spins (triplet state) (Scheme 26).



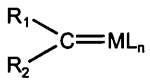
triplet carbene singlet carbene

Scheme 26

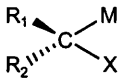
Free carbenes are generally highly reactive and short-lived species. Singlet carbenes add stereospecifically to alkenes but this reaction is often accompanied by competing insertion reactions into C-H bonds. Triplet carbenes react as diradicals and give nonstereospecific addition to alkenes as well as hydrogen abstraction.

However carbenes can be stabilised by a metal thus becoming more suitable for synthetic purposes. Two types of complexes can formally be considered; *viz.* transition metal carbene complexes **18** which have formal metal-carbon double bonds (Scheme 27) and organometallic carbenoids **19** which possess a metal atom M (M = Li, Na,

ZnX, ...) and a leaving group X (X = F, Cl, Br, I, OR, ...) attached at the same carbon centre (Scheme 27).



18



19

Scheme 27

Transition metal carbene complexes of type **18** undergo a wide range of very useful reactions such as alkene metathesis, alkene and alkyne polymerisation, cyclopropanation, insertion reactions and ylide generation. They are the subject of numerous reviews and books.[46]

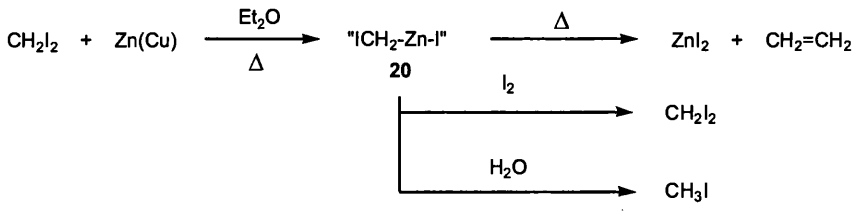
Amongst organometallic compounds of type **19**, we will concentrate on organozinc carbenoids and begin with a very common organozinc carbenoid generated from dihalo compounds, the Simmons-Smith reagent.[47] Since the scope of this carbenoid as well as its use in asymmetric reactions have been intensively reviewed, only a general view of the preparation and reactivity of this reagent will be given.[48,49,8a]

1.2.2 Organozinc carbenoid chemistry

1.2.2.1 From gem-dihalo compounds

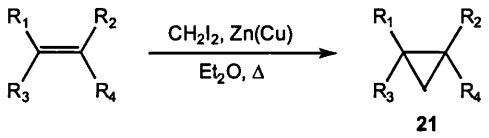
1.2.2.1.1 Background

In 1929, Emschwiller first presented evidence for the formation of iodomethylzinc iodide **20** by the reaction of diiodomethane with zinc-copper couple in ether at reflux.[50] He observed that the organozinc species formed gave methyl iodide upon hydrolysis, diiodomethane by the addition of iodine and evolution of ethylene when the reaction was heated at prolonged reflux (Scheme 28). These observations led Emschwiller to propose that (iodomethyl)zinc iodide **20** had been formed.



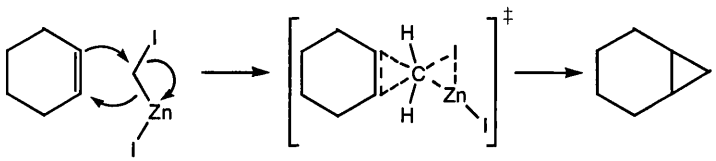
Scheme 28

Almost thirty years after this observation, Simmons and Smith discovered that this new organometallic species could be trapped efficiently by alkenes, thus providing a new and very valuable synthetic route to cyclopropane derivatives **21** (Scheme 29).[51]



Scheme 29

This reaction proved to be stereospecific in terms of strict retention of olefin geometry, usually free from serious side reactions such as C-H insertion reactions and followed second-order kinetics.[51] For these reasons, the Simmons-Smith reaction appeared to transfer a methylene moiety without any free carbene being released. The mechanism proposed for this cyclopropanation reaction proceeds through a "butterfly-type" transition state as depicted in Scheme 30.[51b]

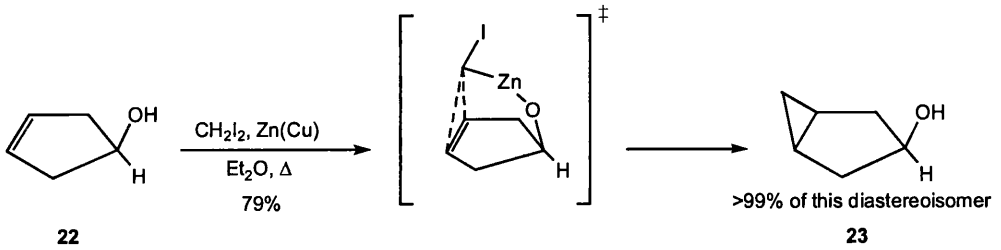


Scheme 30

It was also observed that the zinc reagent behaved as a weak electrophile since it reacted more readily with electron rich olefins.[51]

Another very important characteristic of this reaction is that proximal basic groups (oxygen and nitrogen) could direct the delivery of the methylene group and also enhance the rate of the reaction. The strongly directing effect of oxygen substituents

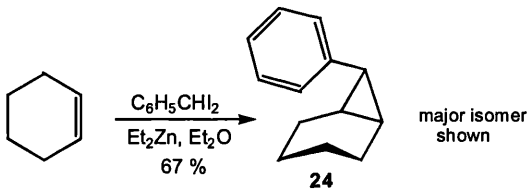
was recognised early on. Thus, Winstein and Sonnenberg showed that the hydroxyl group of 3-cyclopenten-1-ol **22** controlled the stereochemistry of methylene transfer to give exclusively *cis*-3-hydroxybicyclo[3.1.0]hexane **23** (Scheme 31).[52]



22 **23**

Scheme 31

A few years later, Furukawa found that a similar cyclopropanating agent could be generated by an alkyl exchange reaction between diethyl zinc and a 1,1-dihaloalkane.[53] Furukawa's system offers the following advantages over the Simmons-Smith reaction: the reaction is homogenous, reaction times are usually shorter and reactions are not restricted to methylene transfer, but may also be used with alkyl and phenyl carbenoids. For example, the reaction between cyclohexene and benzal iodide in the presence of diethyl zinc affords a mixture of *endo*-**24** and *exo*-**24** in reasonable yield (Scheme 32). The predominant formation of the thermodynamically less favoured isomer is almost always observed for alkylidene and benzylidene transfer.



24

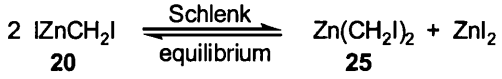
endo:*exo* 17:1

Scheme 32

Since these original observations were made, extensive work has been carried out in order to extend the scope of this reaction and to characterise the cyclopropanating agent.

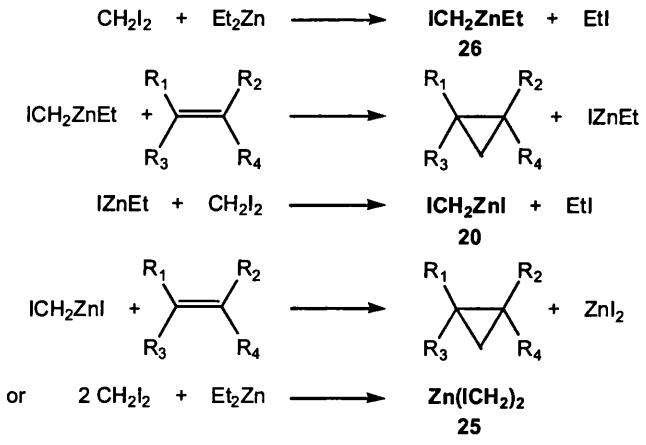
1.2.2.1.2 The "cyclopropanating agent"

The structure of the classical Simmons-Smith reagent, believed to be $IZnCH_2I$ **20** or $Zn(CH_2I)_2.ZnI_2$ **25** (Scheme 33), has been extrapolated from product distribution data (hydrolysis and iodine treatment) and observations of its chemical behaviour.[54]



Scheme 33

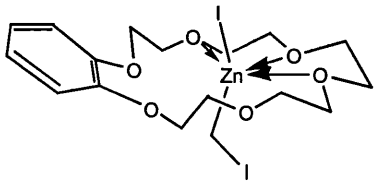
On the other hand the active species in Furukawa's reagent may include species such as ICH_2ZnEt **26**, ICH_2ZnI **20** and/or $Zn(ICH_2)_2$ **25** (Scheme 34).[55]



Scheme 34

X-Ray crystallography and NMR studies have been recently undertaken in order to determine the exact nature of the reactive species involved in both protocols.

Thus, Charette has reported the solid state structure of the $IZnCH_2I$ complex **27** formed by the addition of 1 equivalent of CH_2I_2 to a solution of EtZnI and benzo-18-crown-6 (Scheme 35).[56] As the solution of this complex was still an effective cyclopropanating reagent, he concluded that $IZnCH_2I$ **20** may be the active Simmons-Smith reagent.



27

Scheme 35

A similar conclusion has also been drawn from NMR studies carried out by the same author.[57] Indeed it has been shown that the Schlenk equilibrium, illustrated in Scheme 33, appears to lie heavily on the side of $IZnCH_2I$ as none of the related $Zn(CH_2I)_2$ could be detected by ^{13}C NMR when the experiment was performed in CD_2Cl_2 in the presence of a chiral ether.

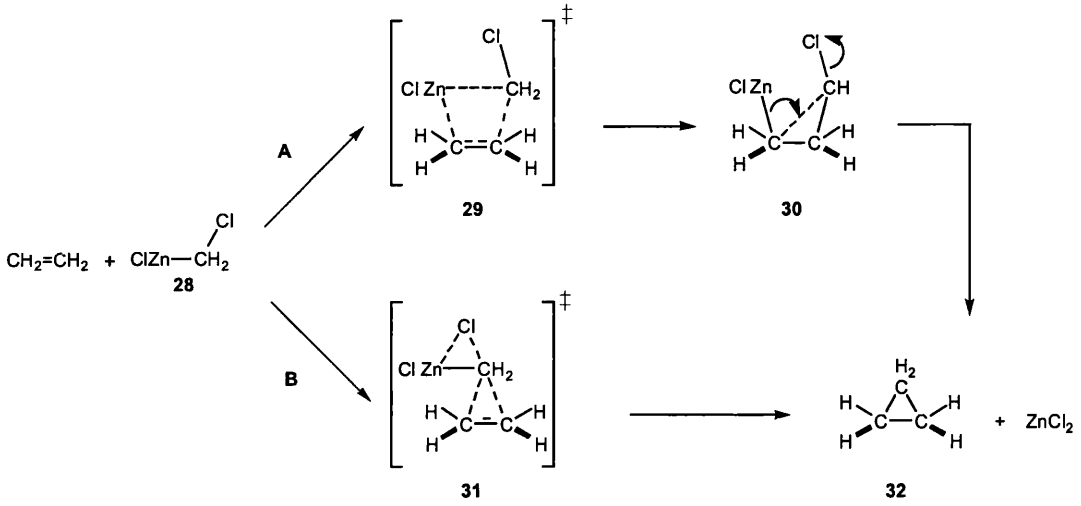
Contrastingly, on the basis of NMR studies, Denmark has noted that Simmons-Smith type reagents exist predominantly as $(ICH_2)_2Zn.ZnI_2$ pairs in acetone solution and thus concluded that this species could be the active reagent in the Simmons-Smith reaction.[58]

These two contradictory conclusions clearly reveal, that at the present time, the exact structural nature of the Simmons-Smith reagent still cannot be unambiguously assigned.

1.2.2.1.3 Theoretical studies on cyclopropanation reactions

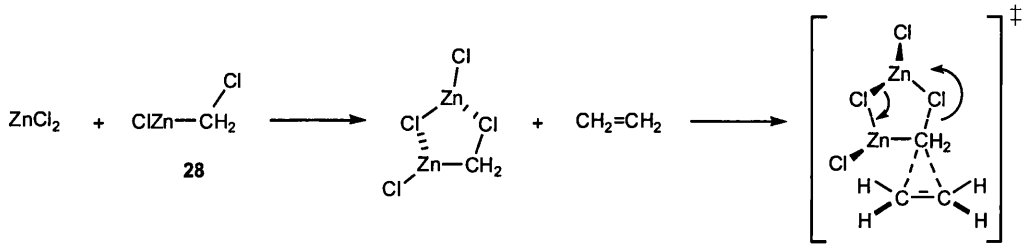
Important computational work has also been done to rationalise the experimental findings.

Thus, cyclopropanation reactions using metal carbenoids can, in general, be considered to follow one of two differing pathways involving either carbometallation or methylene transfer. In the carbometallation pathway (path A), [2+2] addition of the ethylene occurs to produce an intermediate **30** through a four-centred transition state **29** (Scheme 36). A subsequent intramolecular substitution reaction of **30** then affords the cyclopropane product **32**. Alternatively, in the methylene transfer pathway (path B), direct [2+1] addition takes place to provide the cyclopropane ring in a single step through **31** (Scheme 36).



Scheme 36

Through a series of quantum mechanical studies on the cyclopropanation reaction of ethylene and $ClZnCH_2Cl$ **28**, Nakamura *et al.* established that the favoured pathway involved methylene transfer (path B).[59,60] Indeed, the activation energy of the methylene transfer pathway was much lower (17.3 kcal/mol) than that of carbometallation (30.7 kcal/mol). An intrinsic reaction coordinate analysis from **31** back to the reactants also showed that this pathway takes place in two stages, through an initial S_N^2 like displacement reaction by ethylene on halomethylzinc, followed by cleavage of the bond between CH_2 and Zn to give the cyclopropane ring. The ease of the S_N^2 like reaction depends largely on the polarisation of the C-Cl bond. On this point, the authors, using the same model, showed that the Lewis acid ($ZnCl_2$ for their study) acts on the zinc carbenoid reagent to enhance the rate of the methylene transfer reaction (Scheme 37).[60,61]



Scheme 37

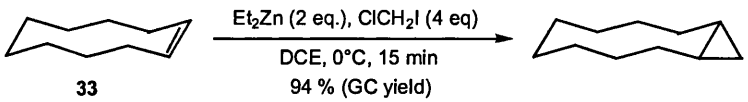
It is important to note that this rate-enhancing effect induced by the addition of zinc salts is in accord with the experimental observations reported both by Wittig[62] and Denmark.[63]

1.2.2.1.4 Evolution of the "cyclopropanating agent"

Many variations of the original Simmons-Smith method, including the use of $Zn/CuCl/CH_2I_2$,[64] Zn(Ag) couple/CH_2I_2,[65] $Zn/TiCl_4/CH_2Br_2$,[66] $Zn/AcCl/CuCl/CH_2Br_2$[67] and Zn/CH_2Br_2 under sonication,[68] have been reported in the literature. Shorter reaction times and better yields are reported for some substrates. A more efficient activation of the zinc seems to be one consistent possible explanation to account for almost all of these results.

However, since the yields in cyclopropanation of unfunctionalised olefins still remain unsatisfactory, further efforts have been made to find an even more reactive cyclopropanating reagent.

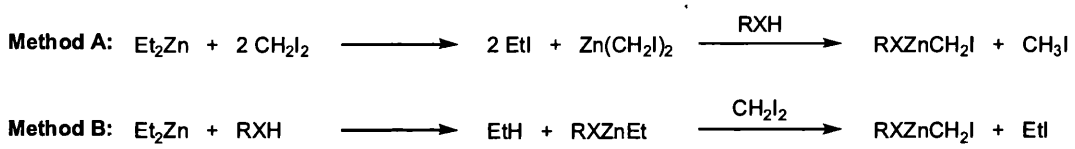
In 1991, Denmark and Edwards showed that the (chloromethyl)zinc reagent, prepared from $ClCH_2I/Et_2Zn$, is generally more reactive that the (iodomethyl)zinc analogue.[69] The most striking result of this study was the 94 % yield (GC yield) obtained with *cis*-cyclodocene **33** with the new reagent in comparison with the 12% using CH_2I_2/Et_2Zn under the same conditions and for the same reaction time (Scheme 38). A noncomplexing solvent such as 1,2-dichloroethane, which is not normally used in organozinc chemistry, was also found to be superior in this reaction.



Scheme 38

The influence of different RX groups in the (iodomethyl)zinc species $RXZnCH_2I$ was then investigated.

The two principal methods employed for the generation of $RXZnCH_2I$ are shown in Scheme 39. In Method A, Et_2Zn is treated with 2 equivalents of CH_2I_2 to form $Zn(CH_2I)_2$, which is subsequently reacted with RXH to give $RXZnCH_2I$. In Method B, Et_2Zn is firstly combined with RXH to form RXZnEt and then reacted with 1 equivalent of CH_2I_2 to generate $RXZnCH_2I$. It is important to note that the various iodomethylzinc species in Scheme 39 are only proposed on the basis of stoichiometry.

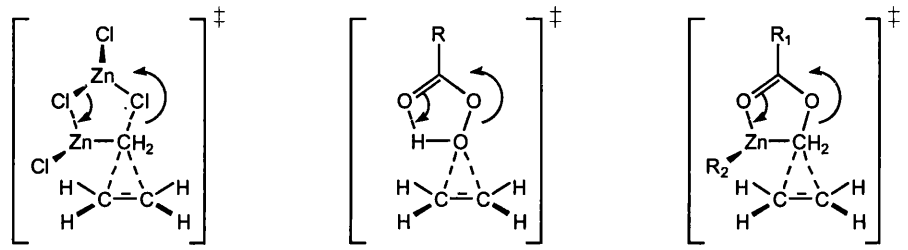


Scheme 39

In this manner, by using Method A, Shi *et al.* investigated the influence of different RX groups and established that as RXH became more acidic, the reactivity of the novel organozinc species increased.[70] The best results were obtained when trifluoro- or trichloroacetic acid were used ($RX = CF_3CO_2$ or CCl_3CO_2) since these reagents display a dramatically increased reactivity towards unreactive olefins, such as *trans*-β-methylstyrene. A study of the cyclopropanating ability of $CF_3CO_2ZnCH_2I$ toward a wide range of alkenes was then undertaken and showed that this reagent is generally very effective. However, it is interesting to note that other authors have discredited the structure of the active species involved in this reaction (*vide infra*).

By the same approach, Charette *et al.* studied the reactivity of new reagents of general structure $ArOZnCH_2I$ ($RX = ArO$) prepared either by Method A or B (Scheme 39).[71] It was observed that carbenoids possessing electron-withdrawing groups on the aromatic ring (F,Cl or Br in position 2,4 and 6) produced very high yields of cyclopropanes. This higher reactivity could result from an increase in the electrophilicity of the zinc carbenoid and this conclusion is in perfect accord with Shi's work.

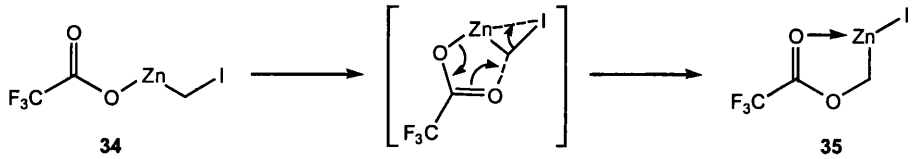
The acyloxymethylzinc carbenoids, recently reported by Charette *et al.*, also appear to be another promising class of cyclopropanating reagents.[72] They were designed having in mind the driving force of the Simmons-Smith reaction catalysed by Lewis acids (*vide supra* 1.2.2.1.3) and the epoxidation reaction using peracids (Scheme 40).



Scheme 40

In this instance, 1:1 mixture of iodomethyl perfluoropentanoate, $C_4F_9CO_2CH_2I$, and diethyl zinc afforded a reactive carbenoid which cyclopropanated efficiently a variety of unfunctionalised olefins, showing the potential of this new reagent. Once again, the presence of an electron-withdrawing group for R_1 in Scheme 40 is expected to increase the electrophilicity of the carbenoid.

In light of this study, Charette has also proposed that the increased reactivity of Shi's carbenoid, $CF_3CO_2ZnCH_2I$, might be attributed to *in situ* equilibration leading to formation of iodomethylzinc trifluoroacetate **35** under the reaction conditions (Scheme 41). This hypothesis was partially verified as the **35**:**34** ratio was evaluated as varying between 2:1 (NMR) and 4:1 (GC analysis).[72]



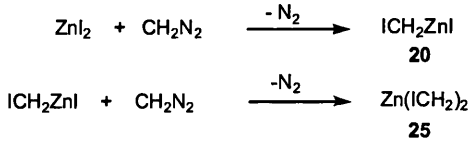
Scheme 41

As evidenced above, through studying the mechanism of the Simmons-Smith reaction, chemists have managed to design more reactive cyclopropanating species. As a direct result the Simmons-Smith reagent and their derivatives can now cyclopropanate

virtually any alkene with high efficiency. However, to date, this methodology is still restricted to the parent methylene carbenoid species.

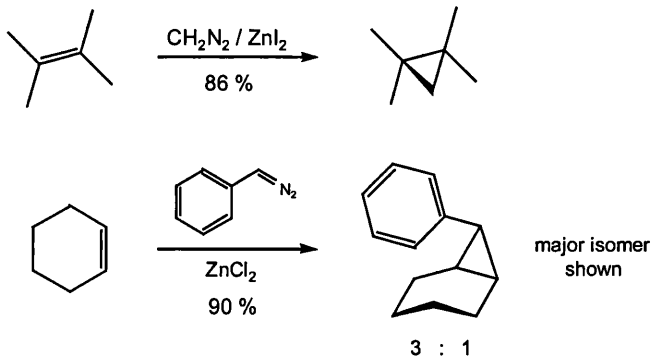
1.2.3.2 From diazoalkanes and zinc salts

An alternative method for the generation of organozinc carbenoids was reported by Wittig in 1959. This method consisted of treatment of an ethereal suspension of a zinc (II) salt ($ZnCl_2$, $ZnBr_2$, ZnI_2, $Zn(OBz)_2$) with diazomethane[62] or aryldiazomethanes.[73] The active cyclopropanating species are believed to be similar to the Simmons-Smith reagent (*vide supra* 1.2.2.1.2) (Scheme 42).



Scheme 42

Thus, a wide range of simple alkenes can be cyclopropanated and the yields are usually good (Scheme 43). In the case of benzylidene transfer the thermodynamically less favoured *endo* isomer is formed predominantly.



Scheme 43

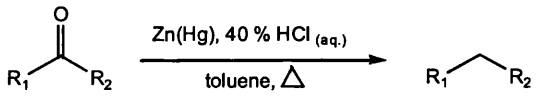
However this approach has received little attention due to the hazards associated with handling diazo compounds.

1.2.3.3 From carbonyl compounds

The generation of organozinc carbenoids from carbonyl compounds is an attractive alternative to the use of dangerous and/or toxic dihalo and diazo precursors. Before describing the evolution of this chemistry within our own group, it is important to recognise the mechanistic parallel which exists with the venerable Clemmensen reduction.

1.2.3.3.1 The Clemmensen reduction of carbonyl compounds

The Clemmensen reduction of ketones and aldehydes originally using amalgamated zinc and hydrochloric acid with an immiscible co-solvent, *i.e.* toluene, is one of the simplest and most direct methods for conversion of the carbonyl group into a methylene group (Scheme 44).[74]



Scheme 44

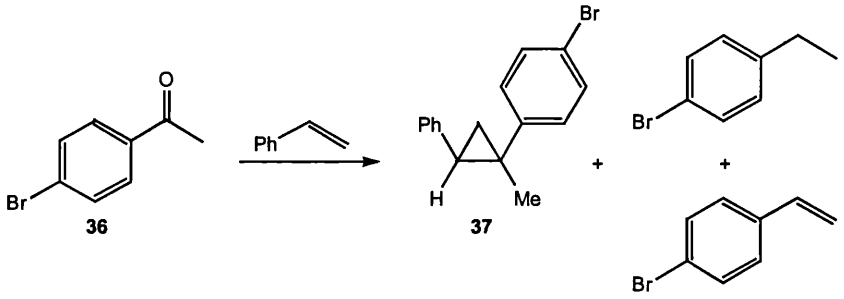
Even though the mechanism of this reaction is not fully understood, the intermediacy of a zinc carbenoid appears to be widely accepted.

One of the first detailed studies into the mechanism of the Clemmensen reduction was performed by Brewster.[75] He proposed that reduction of the carbonyl group took place following 'chemisorption' of the carbonyl group onto the zinc surface followed by delivery of two electrons and the formation of a covalently bonded organozinc species. As alcohols are not generally reduced under Clemmensen conditions, Brewster also suggested that free alcohols were not intermediates in the Clemmensen reduction.

Later work by Nakabayashi supported this proposal, concluding that reduction was a stepwise process involving the generation of organozinc intermediates.[76] He also noted, by investigating the kinetics and the electrochemical reduction of substituted

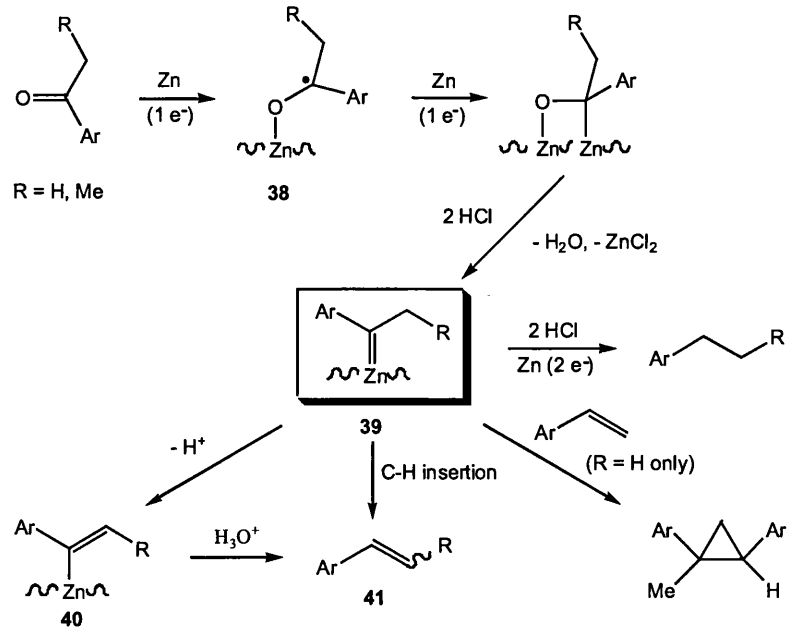
acetophenone, that the electrochemical process could not be directly correlated with the Clemmensen reduction.

In 1986, a study by Burdon provided further indicative results that carbenoid species could be involved in the Clemmensen reduction.[77] Thus when the reaction using acetophenone and substituted acetophenones was performed with amalgamated zinc in 50 % aqueous ethanol self-coupled cyclopropanes were formed. Cross-coupled cyclopropanes can also be obtained by capturing the carbenoid with styrene. Thus 4-bromoacetophenone **36** gave primarily the *cis* cyclopropane **37** with important reductions in the yields of Clemmensen reduction and carbenoid derived products (Scheme 45).



Scheme 45

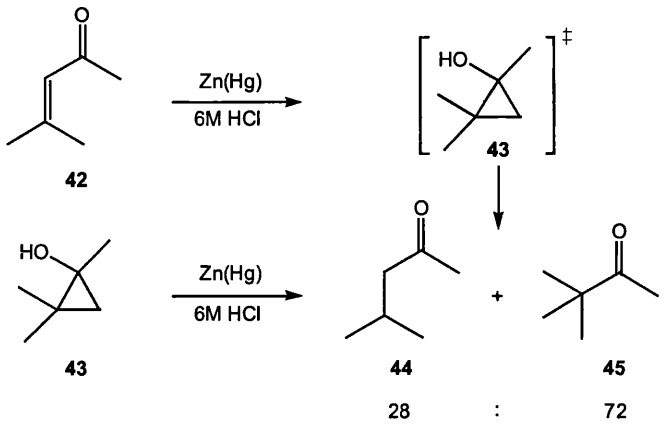
Burdon proposed that all of the above products observed originate from a zinc carbenoid intermediate **39** (Scheme 46). In addition deuterium labelling studies demonstrated that the alkene **41** is formed *via* a vinylic zinc intermediate **40** or directly by C-H insertion reaction.



Scheme 46

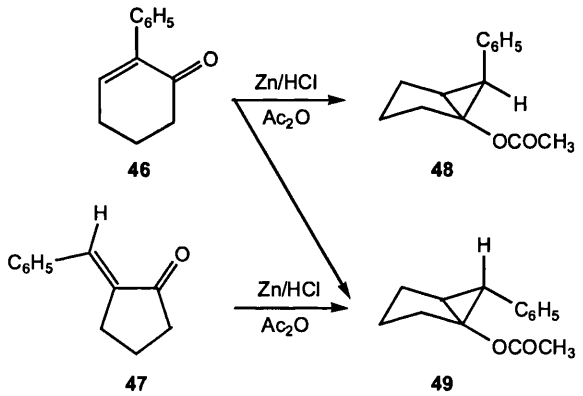
The explanation for the formation of the carbenoid **39** is speculative. The mechanism proposed would also however account for the pinacol type products obtained in Clemmensen reduction since a radical intermediate **38** is involved.

Strong evidence for initial one electron reduction was also provided by the investigation of the Clemmensen reduction of α,β-unsaturated ketones. Davis and Woodgate demonstrated that such reactions proceeded *via* a cyclopropanol intermediate, which, depending upon its mode of ring-opening, can give rise to two structurally isomeric saturated ketones.[78] Thus the Clemmensen reduction of 4-methylpent-3-en-2-one **42** or 1,2,2-trimethylcyclopropanol **43** were found to produce a mixture of **44** and **45** in the same proportion (Scheme 47).



Scheme 47

Similar evidence for one electron reduction was obtained by Elphimoff-Felkin.[79] Indeed performing the reduction of the two cyclic enones **46** and **47** in the presence of acetic anhydride allowed the isolation of the bicyclic acetate intermediates **48** and **49** (Scheme 48).



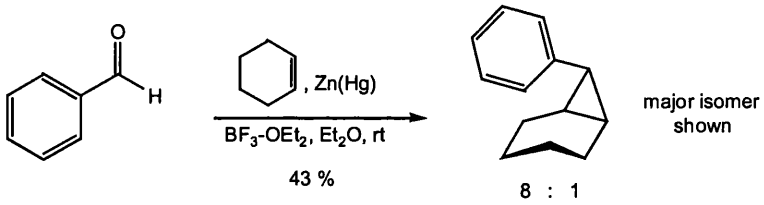
Scheme 48

Although a carbenoid species seems to be involved in the Clemmensen reduction, classical carbenoid reactivity is not routinely observed since the vigorous reaction conditions employed favour its further two electron reduction and protonation to deliver the methylene group.

Hence, in order to exploit the synthetic potential of such carbenoids, alternative reaction conditions are required which preclude these latter steps.

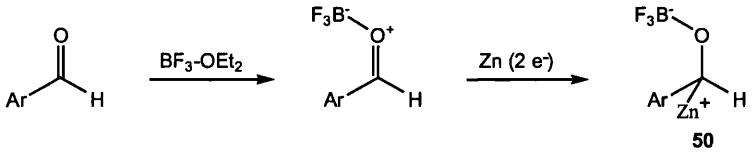
1.2.3.3.2 The controlled generation of organozinc carbenoids from carbonyl compounds

Elphimoff-Felkin and Sarda first proposed, in 1969, to replace the protons responsible for the rapid destruction of the carbenoid by a Lewis acid.[80] Thus, by performing a reaction with boron trifluoride diethyletherate in a dry solvent they demonstrated that the carbenoid generated from aromatic aldehydes could be trapped by an alkene to yield a cyclopropane (Scheme 49). It is worth noting that cyclic alkenes gave the more hindered *endo* isomer preferentially. This particular feature seems to be inherent in benzylidene transfer (*vide supra* 1.2.2.1.1 and 1.2.2.2).



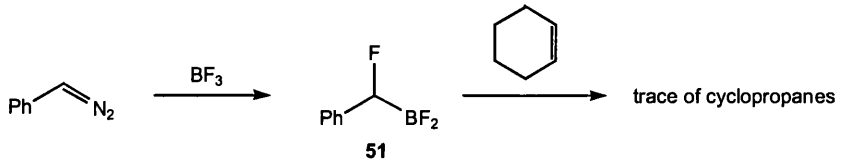
Scheme 49

The species **50** was proposed to be the carbenoid involved in this reaction (Scheme 50).



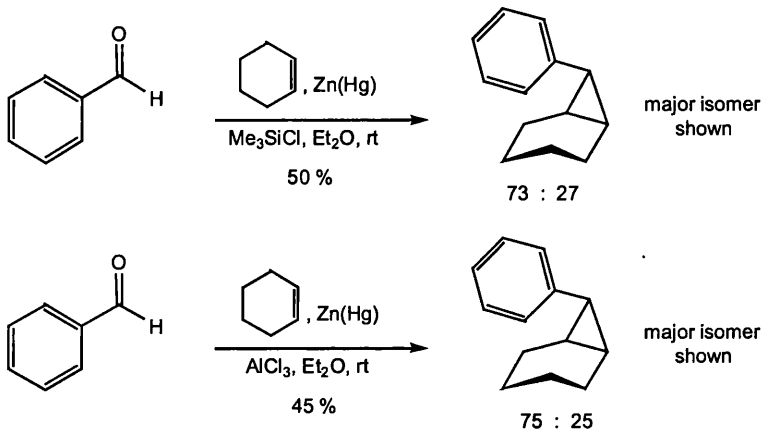
Scheme 50

Interestingly, the same authors also reported that the reaction of phenyldiazomethane in the presence of boron trifluoride afforded just traces of the expected cyclopropanes, which can rule out the possibility of **51** as the reactive intermediate (Scheme 51).



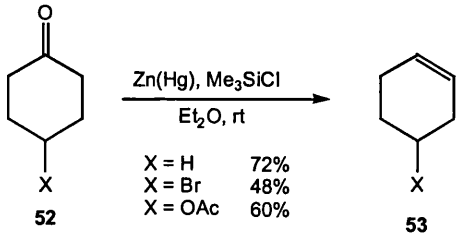
Scheme 51

In 1975, Elphimoff-Felkin and Sarda also briefly studied the reactivity of carbenoids, generated from benzaldehyde, using other oxophilic electrophiles.[81] Whilst no cyclopropanation reaction was observed with magnesium bromide diethyletherate, chlorotrimethylsilane and aluminium trichloride both produced 7-phenylnorcarane in moderate yield (Scheme 52).



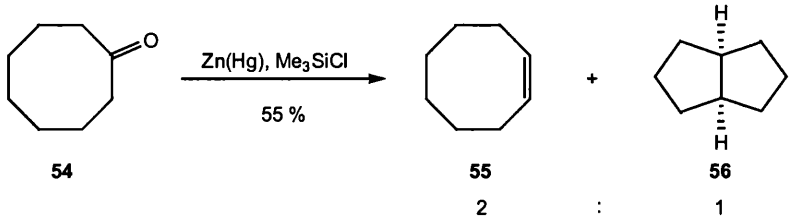
Scheme 52

In 1973 Motherwell discovered that cyclohexanones **52**, in the presence of zinc and chlorotrimethylsilane, were efficiently converted to the corresponding cyclohexenes **53** (Scheme 53).[82]



Scheme 53

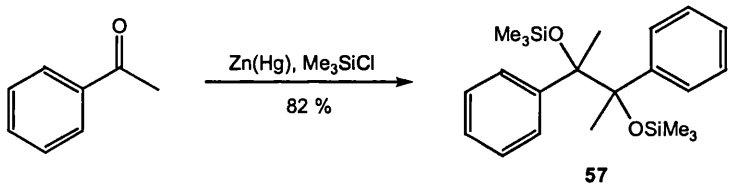
Particularly indicative of the intermediacy of a carbenoid species was the case of cyclooctanone **54** which furnished not only *cis* cyclooctene **55** but also bicyclo[3.3.0]octane **56** as a result of transannular insertion of the carbenoid (Scheme 54).



Scheme 54

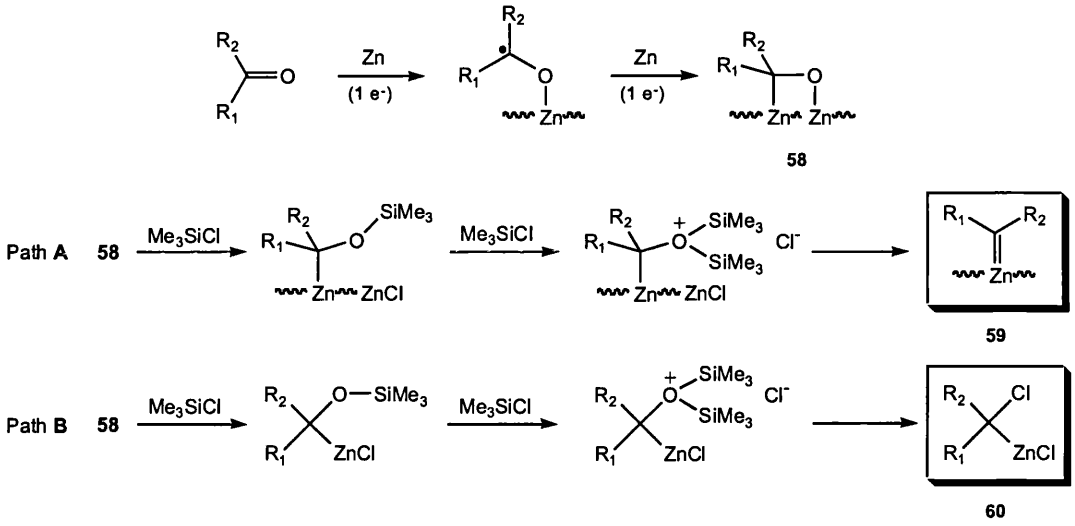
It is also important to note that the behaviour of this carbenoid is similar to that encountered in the Clemmensen reduction, since a similar C-H insertion reaction had been reported.[74]

Of equal interest was the observation that the reaction of acetophenone provided the pinacolic product, 2,3-diphenyl-2,3-di(trimethylsilyloxy) butane **57**, in 82 % yield (Scheme 55). This emphasises the similarity of the pathway to carbenoid generation with that proposed by Burdon for the Clemmensen reduction (*vide supra* 1.2.2.3.1).



Scheme 55

Thus the formation of the organozinc carbenoid from a carbonyl group in the presence of zinc and chlorotrimethylsilane can be expected to occur by a pathway which is similar to carbenoid formation under Clemmensen conditions. Bearing in mind the mechanism proposed by Burdon[77] for the Clemmensen reduction (*vide supra* 1.2.2.3.1), one can expect that the carbonyl group successively receives two electrons from the zinc to generate the organozinc intermediate **58** and that the oxophilic chlorotrimethylsilane serves as a direct substitute for the proton in the mechanism of Clemmensen reduction (Scheme 56). The final organozinc carbenoid can then be viewed, either as a species bonded to the zinc surface **59** (path A), as postulated by Burdon[77], or as a tetrahedral chloro congener **60** by analogy with the Simmons-Smith reagent[51] (path B).

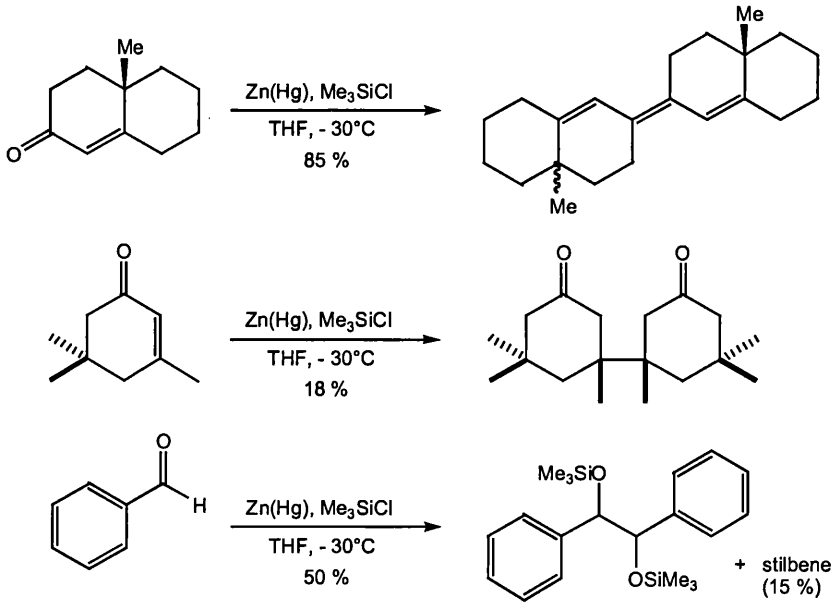


Scheme 56

1.2.3.3.3 Evolution of organozinc carbenoid chemistry within our group

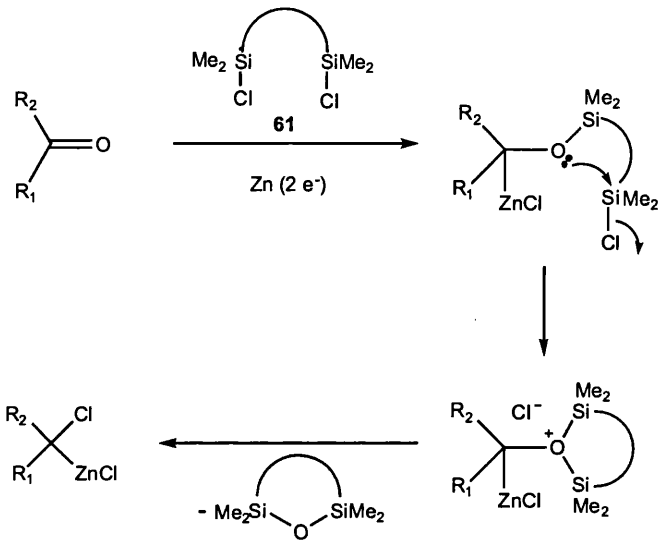
Following on from the observation that dicarbonyl coupling of certain aryl and α,β-unsaturated carbonyl compounds can be achieved under Clemmensen conditions, Motherwell, in collaboration with Banerjee's group, investigated the possibility of performing similar reactions using the zinc/chlorotrimethylsilane system.[83]

Although good results were obtained with certain enones, pinacolic coupling and dimerisation at the softer β-carbon atom were the major reactions observed for other substrates (Scheme 57).



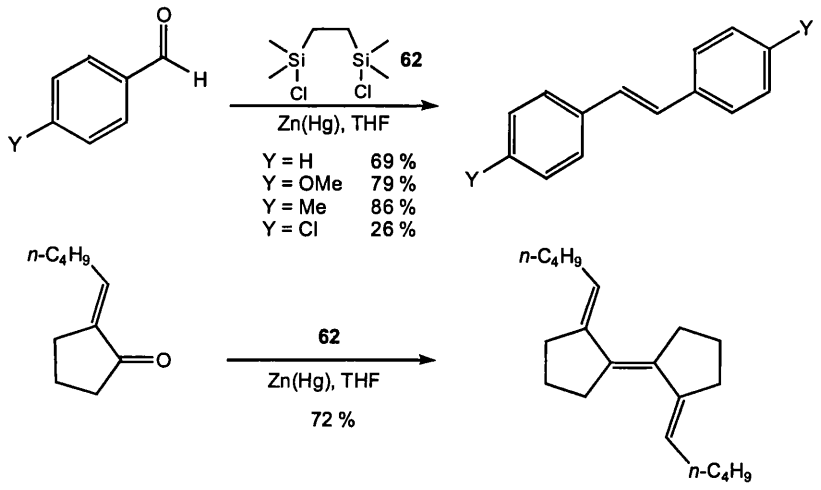
Scheme 57

These side reactions are presumably due to the longevity of the carbon centred radicals produced by a single electron transfer from zinc (*vidra supra* 1.2.2.3.1). In order to combat this problem, since the overall stoichiometry of carbenoid generation requires two molecules of chlorotrimethylsilane per carbonyl group, a bis-silicon electrophile **61** which would allow intramolecular delivery of the second silicon electrophile and hence facilitate carbenoid generation was selected (Scheme 58).[84]



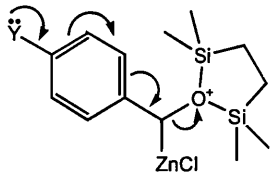
Scheme 58

The use of 1,2-bis (chlorodimethylsilyl) ethane **62** as the bis-silicon electrophile in the symmetrical coupling reaction led to an improvement in yield which was especially significant for aromatic carbonyl compounds (Scheme 59).[84]



Scheme 59

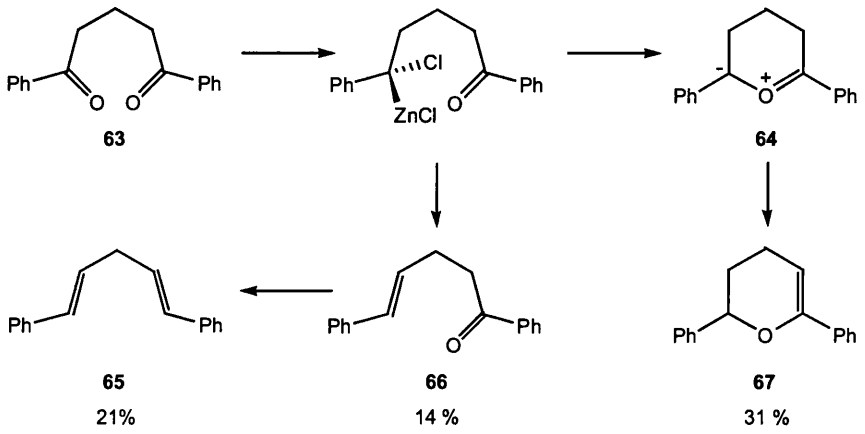
From the results obtained in the aromatic aldehyde series, it seems reasonable to think that an electron donating group in the *para* position to the aldehyde may promote expulsion of the cyclic siloxane, as implied in Scheme 60 and hence accelerate carbenoid generation.



Scheme 60

To understand the mechanism of the dicarbonyl coupling reaction, it is worth noting that neither vicinal diols nor their silylated derivatives can be converted to olefins using the zinc/chlorotrimethylsilane system. However, under the same conditions, it has been observed that stilbene epoxides led to alkene formation, implying that epoxides are viable intermediates.

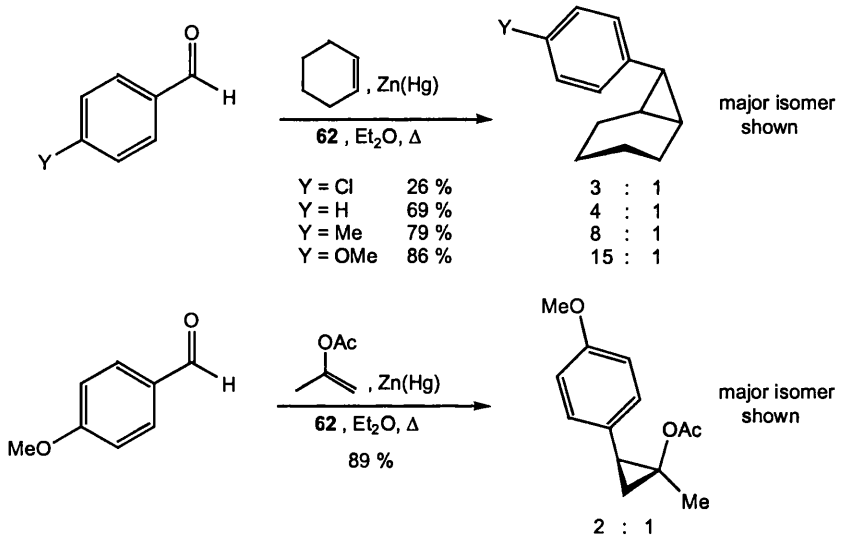
It is reasonable to envisage in turn that these epoxides can be derived from a carbonyl ylide intermediate. Indeed the attempted intramolecular dicarbonyl coupling of **63** afforded the dihydropyran **67** along with the alkene **66** and the diene **65** (Scheme 61). Formation of the dihydropyran may be rationalised as proceeding *via* the carbonyl ylide **64**, which fails to close to an epoxide by virtue of a combination of electronic effects and ring strain.



Scheme 61

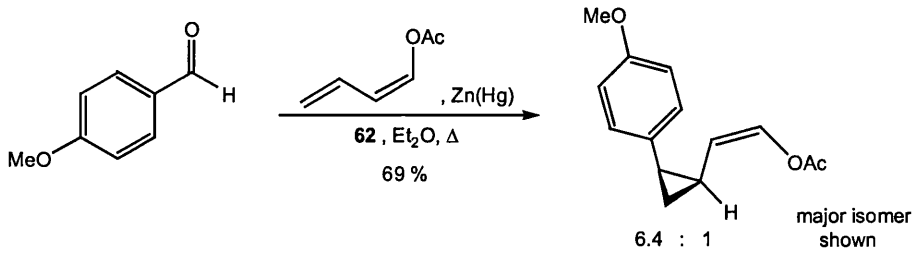
As a logical extension to this work, Motherwell and Roberts investigated the cyclopropanating ability of this type of carbenoid.[85]

They found that a series of simple alkenes and enol acetates could be readily cyclopropanated by the carbenoids derived from a range of *para* substituted arylaldehydes (Scheme 62). As already noted, the more hindered *cis* or *endo* isomers were predominant and yields were best for electron rich aromatic aldehydes.[86]



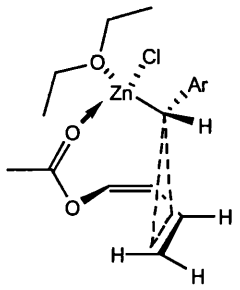
Scheme 62

A range of organozinc carbenoids generated in a similar fashion can also be trapped efficiently by *Z*-1-acetoxybutadienes thus yielding functionalised vinylcyclopropanes, as illustrated by the example shown in Scheme 63.[87]



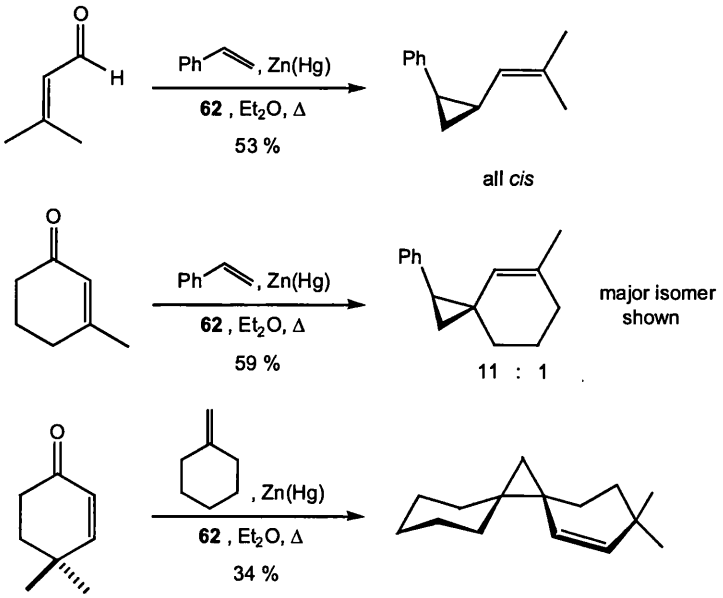
Scheme 63

The complete regioselectivity and the high *cis* selectivity observed support the idea that the cyclopropanation reaction is directed by the acetoxy group as depicted in Scheme 64. As mentioned previously, similar observations have also been reported with the Simmons-Smith reagent (*vide supra* 1.2.2.1.1).



Scheme 64

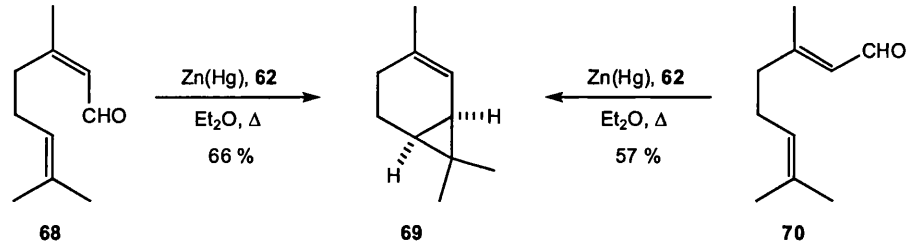
Interestingly and in apparent contrast to the studies of both Woodgate[78] and Elphimoff-Felkin[79], it was shown that α,β-unsaturated organozinc carbenoids, known to undergo reductions of the double bond or rearrangements under Clemmensen reduction (*vide supra* 1.2.2.3.1), can also be trapped by alkenes to yield cyclopropanes if they are generated using the zinc/bis-silicon electrophile system (Scheme 65).



Scheme 65

Curiously however, certain simple unsubstituted α,β-unsaturated carbonyl compounds, such as cyclohexenone or cyclopentenone, failed to give cyclopropanes under the same conditions. This observation suggests that some degree of substitution either at or around the β carbon of the unsaturated carbonyl group is required (*vide infra*).

During a study of intramolecular cyclisation using this methodology, Motherwell and Roberts found that efficient cyclopropanation could occur even when the initial geometry around the α,β-unsaturated carbonyl group was unfavourably located with respect to the alkene trap.[88] Thus, Δ^2-carene **69** can be synthesised starting either from neral **68** or from the monoterpene geranial **70** in comparable yield (Scheme 66).



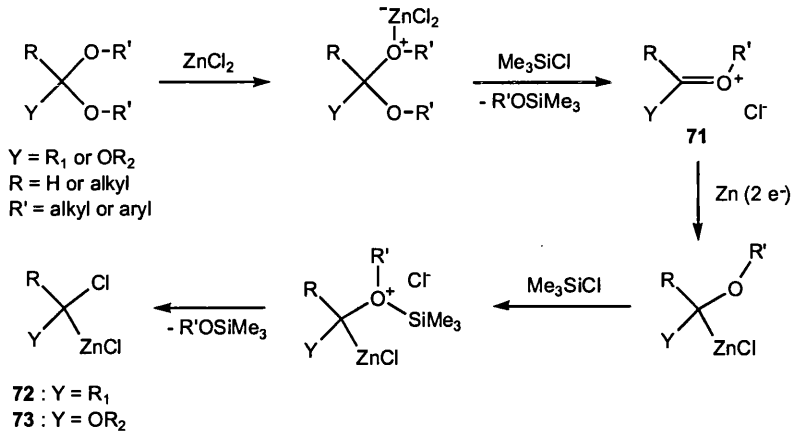
Scheme 66

This result, when taken in conjunction with the necessity for some degree of steric hindrance around the β carbon, suggests that 1,3-allyl migration of the carbon zinc bond can occur to relieve congestion, but with consequent loss of alkene geometry (Scheme 67).

Scheme 67

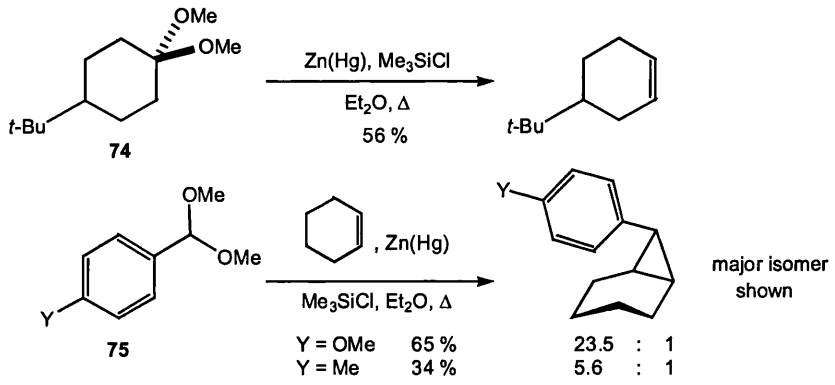
More recently, Motherwell and Popkin demonstrated that organozinc carbenoids could also be generated from acetals, ketals[89] and orthoformates.[90] From a mechanistic standpoint, and in contrast to the reactions of the carbonyl group which are postulated to involve initial formation of a zinc-oxygen bond, these transformations may proceed *via*

an oxonium intermediate **71** before evolving to the organozinc carbenoid **72** or the α-alkoxy- or α-aryloxyorganozinc carbenoid **73** (Scheme 68).



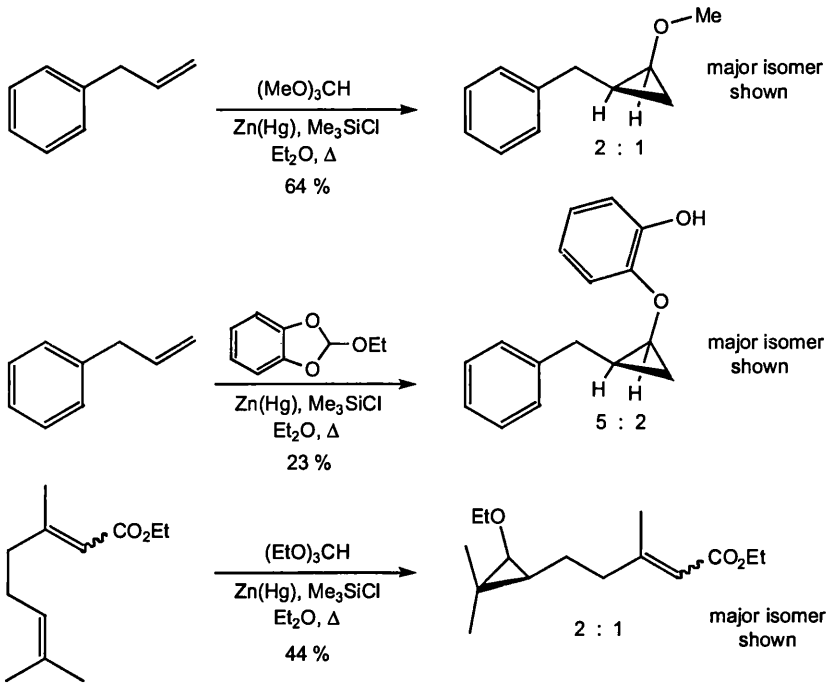
Scheme 68

Thus ketal **74** was found to give the corresponding alkene *via* a C-H insertion reaction and aryl acetals **75** furnished cyclopropanes (Scheme 69).[89]



Scheme 69

In terms of generating functionalised organozinc carbenoids, the selection of an orthoformate as reagent provided a series of alkoxy- and aryloxycyclopropanes in a method which avoided the handling of highly toxic α-halo or α-dihaloethers (Scheme 70). Surprisingly such carbenoids, which should exhibit nucleophilic character, seem to react preferentially with electron-rich alkenes (last example in Scheme 70).[90]



Scheme 70

1.3 Summary and perspectives

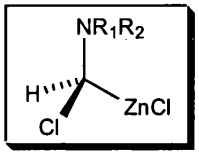
The foregoing introductory overviews have hopefully highlighted several important aspects both in current methodology for aminocyclopropanes construction and in recent advances in the generation and reactivity of organozinc carbenoids. In particular, for both of these areas, it should be emphasised that simple and effective methods for the addition of heteroatom functionalised carbenoids to alkenes are not generally used by the synthetic organic chemist, who continues to consider that the use of organozinc carbenoids invariably involves methylene transfer and that the copper or rhodium catalysed addition of diazo esters to alkenes allows for functionalised carbenoid addition. Clearly, considerable scope therefore exists for progress in this area.

Chapter 2

Results and Discussion

2 Introduction

The following programme of research was initiated with the objectives of studying the generation and the behaviour of hitherto unknown organozinc carbenoids possessing nitrogen functionalities attached to the carbenoid carbon (Scheme 71).

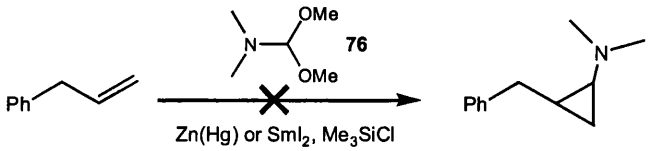


Scheme 71

As we shall see, the primary discovery that such species, when attached to a cyclic amide, can cyclopropanate alkenes efficiently led us to an exciting quest toward the development of a versatile method for the preparation of chiral primary aminocyclopropanes. Throughout this study, our curiosity drove us to investigate original sequences for the synthesis of structurally interesting compounds such as *trans* amino cyclopropanols and *N*-substituted cyclopropyl amino acids.

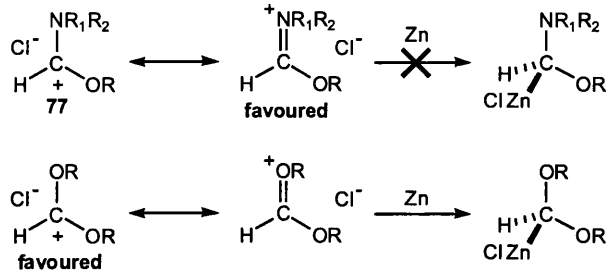
2.1 Background – The attempted aminocyclopropanation reaction using dimethylformamide dimethyl acetal

The starting point for the work presented in this thesis follows an initial study of the attempted synthesis of aminocyclopropanes carried out by Popkin.[91] Indeed, as an extension of their work on alkoxycyclopropanation reactions using orthoformates,[90] Motherwell and Popkin recognised the potential for a similar generation of aminocarbenoids from dimethylformamide dimethylacetal **76**. However, in the presence of chlorotrimethylsilane, using either zinc amalgam or samarium diiodide as the electron source, no cyclopropanation reaction occurred with allylbenzene (Scheme 72).



Scheme 72

Thus, when compared to an aryl or an alkoxy group, the selection of the dimethylamino moiety has an evident negative impact on the potential generation, stability and/or the reactivity of the putative carbenoid species. In particular, we considered that a possible problem might lie in the ability of zinc to deliver two electrons to the amino substituted carbenium ion **77** as compared with the successful reduction of the oxonium ion in the alkoxycyclopropanation (Scheme 73).



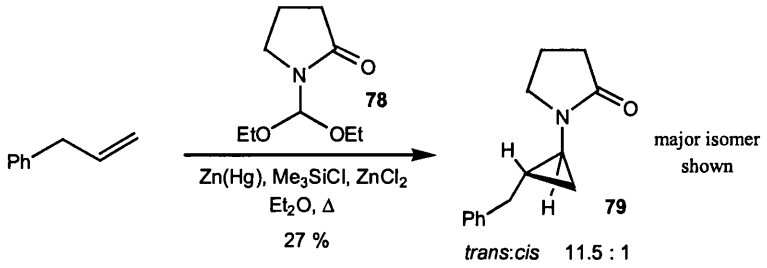
Scheme 73

This situation would arise naturally as a consequence of the fact that the nitrogen atom is less electronegative and hence able to "neutralise" the positive charge on the adjacent carbocation more effectively than an oxygen atom. With this perspective in mind, we therefore decided to attenuate the strong electron-donating ability of the nitrogen lone pair by addition of an adjacent electron-withdrawing group. Interestingly, such an approach has been applied to Fisher aminocarbenes and has shown that the complexes become more similar to alkoxycarbenes in character.[92]

2.2 Preliminary study on the amidocyclopropanation reaction using *N*-diethoxymethyl-2-pyrrolidinone as the carbenoid precursor

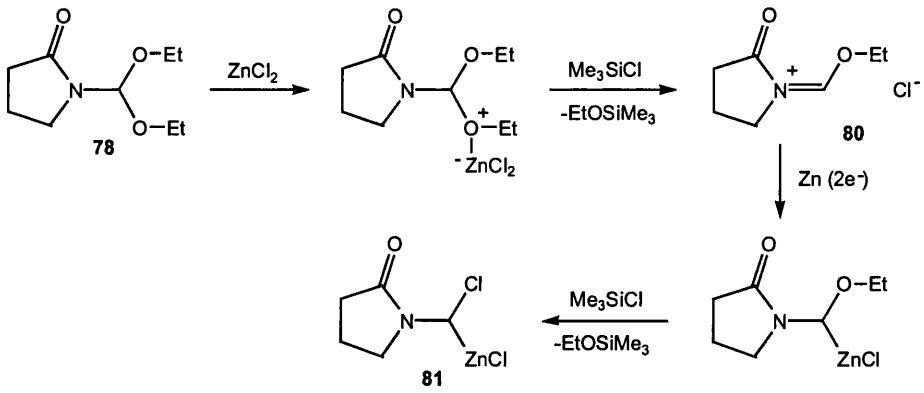
In order to examine the above hypothesis, the cyclopropanating ability of the carbenoid generated from *N*-diethoxymethyl-2-pyrrolidinone **78** was accordingly investigated. The required substrate was very simply prepared in 70 % yield by reaction of 2-pyrrolidinone with triethylorthoformate in the presence of a catalytic amount of aluminium chloride.[93]

To our delight, when the reaction between **78** and allylbenzene was first attempted under the same experimental conditions as used for alkoxycyclopropanation,[91] the desired product **79** was obtained, albeit in low yield (Scheme 74). Contrary to the usual stereoselectivity observed in a cyclopropanation reaction involving an organozinc carbenoid (*vide supra*), the *trans* isomer was formed predominately.



Scheme 74

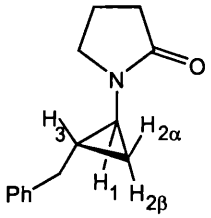
From a mechanistic standpoint, a plausible sequence for the formal generation of the α-amidoorganozinc carbenoid from **81** is shown in Scheme 75 and involves Lewis acid assisted cleavage of one ethoxy group by chlorotrimethylsilane and subsequent two electron reduction of the resultant acyliminium ion **80** (or its covalent congener). Reaction with a second equivalent of chlorotrimethylsilane then furnishes carbenoid **81**.

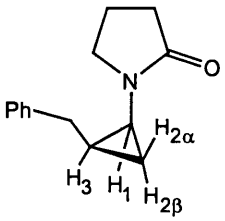


Scheme 75

2.3 Methods used to determine the stereoselectivity of the cyclopropanation reaction

The stereochemistry of the two cyclopropanes obtained from the above reaction was determined by NMR spectroscopy. After assigning the signals of cyclopropyl protons, their coupling constants were examined and the relationship between them determined. From the Karplus equation, the values of the coupling constants of vicinal protons are larger for *cis* couplings than for *trans* couplings.[94] As usual for cyclopropane rings, the geminal coupling constant $^2J_{2\alpha\text{-}2\beta}$ was in the typical range of 4.5-6.5 Hertz (Table 1).





	***trans* isomer**		***cis* isomer**	
	J (Hz)	Relationship	*J* (Hz)	Relationship
$J_{2\alpha-2\beta}$	5.8	geminal	6.0	geminal
$J_{1\text{-}2\alpha}$	4.1	*trans*	4.6	*trans*
$J_{1\text{-}2\beta}$	7.5	*cis*	8.0	*cis*
$J_{1\text{-}3}$	3.5	*trans*	7.0	*cis*
$J_{2\alpha\text{-}3}$	9.4	*cis*	6.3	*trans*
$J_{2\beta\text{-}3}$	6.1	*trans*	8.8	*cis*

Table 1

The determination of the stereochemistry for other cyclopropanes described in the present thesis has been made in a similar manner. In some cases, NOESY experiments were carried out to confirm their assignments in an unambiguous way. Detailed characterisation of the molecules presented can be found in the Experimental section.

2.4 Further study on the amidocyclopropanation of allylbenzene using *N*-diethoxymethyl-2-pyrrolidinone as the carbenoid precursor

As the yield obtained from the exploratory reaction between allylbenzene and **78** was relatively low, further improvements were required.

The optimisation of the amidocyclopropanation reaction began with the study of the influence of the ratio of the amount of alkene to the carbenoid precursor employed (Table 2).

A typical experimental procedure involved slow addition of a solution of *N*-diethoxymethyl-2-pyrrolidinone **78** in diethyl ether to a suspension of zinc amalgam (10 eq / carbenoid precursor), chlorotrimethylsilane (5 eq / carbenoid precursor), anhydrous $ZnCl_2$ (1 eq / carbenoid precursor) and allylbenzene in diethyl ether at reflux.

	Alkene (eq)	Carbenoid precursor (eq)	Yield
1	2	1	60 %
2	4	1	68 %
3	1	2	88 %

Table 2

From this study it appears that the carbenoid species which derived from **78** could be efficiently trapped by allylbenzene (entries 1-3), and when a two-fold excess of carbenoid precursor relative to the alkene was used, the desired product was obtained in very high yield (entry 3).

Surprisingly, it was noticed that during the addition of the *N*-diethoxy amide **78** the zinc amalgam gradually formed soft balls before ending as a gum like substance. As this observation had no precedent in the history of the study of organozinc carbenoids within our group, an interaction between the nitrogen functionality and the zinc was suspected. As the early formation of some form of zinc aggregate is likely to result in a diminution of the surface area and hence the reaction conversion rate, we were therefore interested to investigate the experimental parameters which can have a direct influence on the physical stability of the zinc amalgam.

Initially, it was found that a very slow addition (*ca* 0.1 mmol / hour) of a solution of *N*-diethoxymethyl-2-pyrrolidinone **78** greatly delayed the aggregation of the zinc. The use of THF as solvent or co-solvent with diethyl ether also suppressed the formation of zinc balls although ring-opening by-products from THF arose during such reactions, leading to some difficulties in the isolation of pure product.

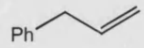
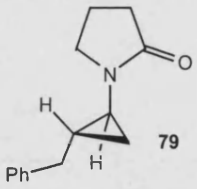
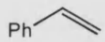
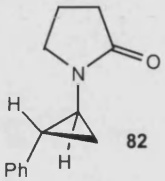
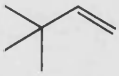
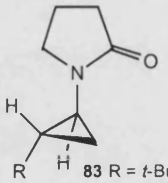
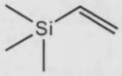
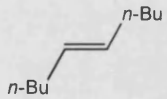
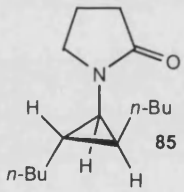
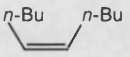
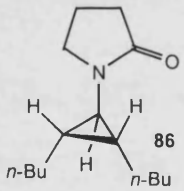
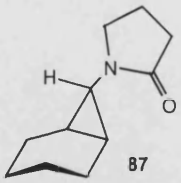
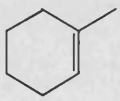
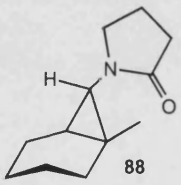
Surprisingly, the presence of zinc chloride also proved to be very important to ensure an increase in the stability of the zinc amalgam. If the reaction was performed without zinc chloride, hard zinc balls were formed at a very early stage during the addition of the diethoxymethyl amide **78**. When a catalytic amount of zinc chloride (0.25 eq / carbenoid precursor) was employed, the zinc quickly formed a gum. As a consequence, the use of stoichiometric quantities of $ZnCl_2$ and carbenoid precursor appeared to produce the best results.

Thus, having now an efficient procedure for performing amidocyclopropanation reactions, our attention was then directed towards a study of the scope of this reaction.[95]

2.5 Scope and limitation of this novel amidocyclopropanation reaction

2.5.1 Cyclopropanation of unfunctionalised alkenes

A typical experimental procedure involved slow addition of a solution of *N*-diethoxymethyl-2-pyrrolidinone **78** (2 eq) in diethyl ether to a suspension of vigorously stirred zinc amalgam (20 eq), chlorotrimethylsilane (10 eq), anhydrous $ZnCl_2$ (2 eq) and an alkene (1 eq) in diethyl ether at reflux. These conditions were examined for a range of alkenes as shown in Table 3.

	Alkene	Product	Addition / reaction time	Isomer ratio[a] *trans*:*cis*	Yield
1		 **79**	14 h / 6 h	11.5:1	88 %
2 a		 **82**	14 h / 6 h	1.1 :1	49 %
2 b			2 h / 12 h[b]		70 %
3 a		 **83** R = *t*-Bu **84** R = $SiMe_3$	14 h / 6 h	>95:<5	61 %
3 b			16 h / 6 h	>95:<5	58 %
4		 **85**	16 h / 6 h	—	83 %
5		 **86**	14 h / 6 h	1:1	52 %
6		 **87**	16 h / 6 h	10:1	66 %
7		 **88**	16 h / 6 h	1.3:1	63 %

[a] Determined using ^{1}H NMR spectroscopy. [b] Performed at room temperature. For convenience, only the *trans* isomer is shown.

Table 3

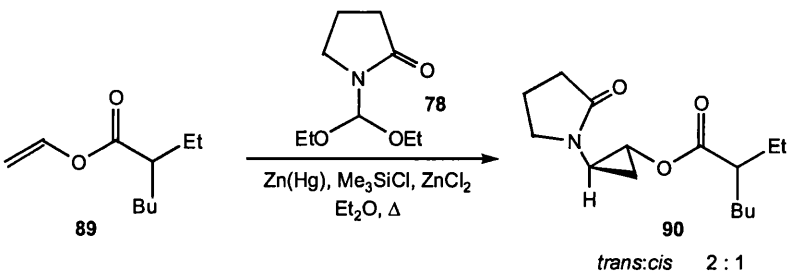
Further examination of the results in Table 3 confirms that preparatively useful yields of amidocyclopropanes can be obtained from mono- (entries 1-3), di- (entries 4-6) and tri- (entry 7) substituted alkenes and that reaction occurs with retention of the original alkene geometry (entries 4 and 5). Although the stereochemical outcome of these reactions can clearly be influenced by substrate structure (compare entries 1 and 2), it is also significant that there is a distinct preference for the formation of the less hindered *trans* (or *exo*) isomer (entries 1-3, 6 and 7), which is even more evident when the alkene bears a bulky group (entries 3a and 3b).

It is also important to note that the standard procedure initially failed to give a satisfactory yield for the amidocyclopropanation reaction of styrene as dimers and cyclopropanated dimers were obtained along with the desired product (entry 2a). The formation of these by-products was suppressed by shortening the addition time of the carbenoid precursor and thus the yield of the cyclopropanated product was improved from 49% to 70% (entry 2b).

2.5.2 Cyclopropanation of functionalised alkenes

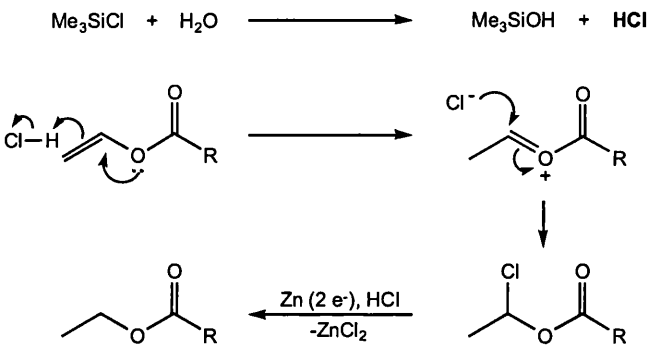
2.5.2.1 Cyclopropanation of electron rich double bonds

As in the study of the alkoxycyclopropanation reaction,[91] simple enol esters, such as isopropenyl acetate, failed to yield the desired product in contrast to the enol ester **89** possessing a bulkier alkyl chain (Scheme 76). Due to the presence of a chiral centre **90** was obtained as a mixture of two *trans* and *cis* isomers. The ratios between the two isomers *trans* and the two isomers *cis* have appeared to be equal as determined by ^{1}H NMR.



Scheme 76

When the cyclopropanation of **89** was first attempted, the reaction proceeded in 31% yield. On examination of the ^{1}H NMR of the crude reaction mixture, the major product obtained appeared to be the reduced starting material (Table 4, entry 1). At this stage, it was the first time that an alkene was reduced under our experimental conditions. This surprising result shows that although every effort was made to perform the reaction under strictly anhydrous conditions, hydrogen chloride was generated during the reaction and this particular alkene was prone to being reduced, presumably through the sequence presented in Scheme 77.



Scheme 77

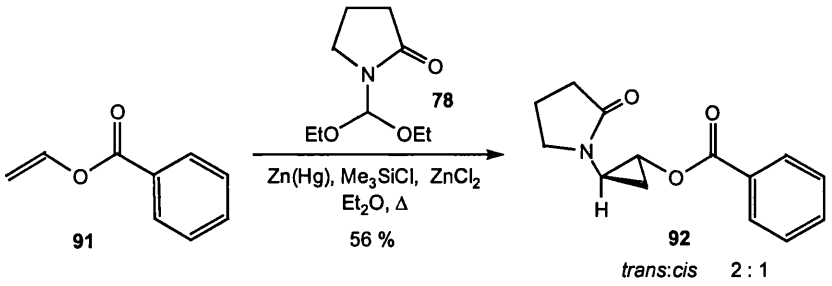
Efforts were then made to optimise this reaction. Shortening of the addition time allowed us to improve the yield of this reaction to 57% (Table 4, entry 3). However, if the addition of the solution of **78** was too rapid, the zinc tended to form a gum within the first hour of the addition leading to a dramatic reduction in the zinc contact surface and this effect, in turn, could explain the observed decrease in the amount of starting material cyclopropanated (Table 4, entry 2).

	Addition time / temperature	Reaction time / temperature	Yield	Ratio of[a]		
				SM	Reduced SM	Product
1	6 h at reflux	14 h at rt	31%	5	45	50
2	2.5 h at reflux	14 h at rt	45%	20	15	75
3	4 h at reflux	14 h at rt	57%	5	10	85

[a] Determined from the crude reaction mixture after work-up using ^{1}H NMR spectroscopy.

Table 4

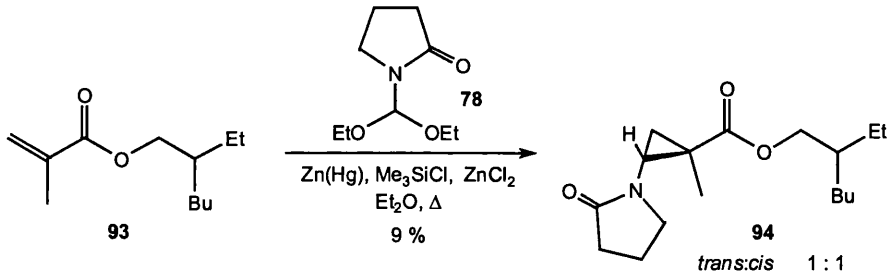
By following similar experimental conditions, vinyl benzoate **91** was cyclopropanated in comparable yield (Scheme 78).



Scheme 78

2.5.2.2 Cyclopropanation of electron deficient double bonds

Although no cyclopropanation reaction was observed using methyl cinnamate, the acrylate derivative **93** was cyclopropanated, albeit in very low yield (Scheme 79).



Scheme 79

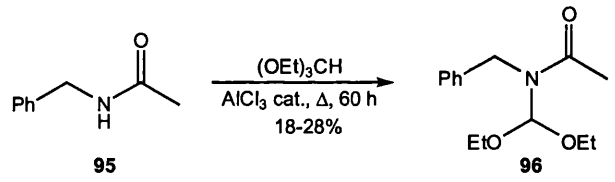
Thus, from these results, electron deficient double bonds appear less likely to be cyclopropanated than electron rich ones, indicating that chemoselective cyclopropanation of electron rich double bonds in the presence of electron deficient double bonds is conceivable.

2.6 Extension of this novel amidocyclopropanation reaction

2.6.1 Study of the amidocyclopropanation reaction using *N*-benzyl-*N*-diethoxymethylacetamide as the carbenoid precursor

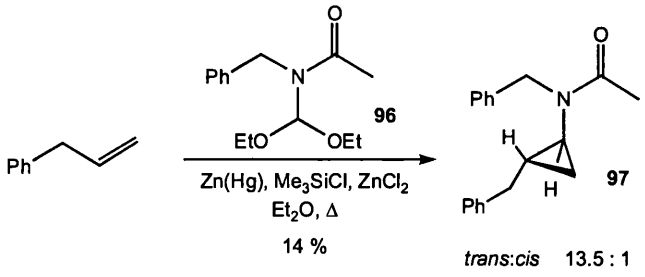
We were then interested in extending the newly developed amidocyclopropanation reaction to different carbenoid precursors. Initially our attention was focused on the *N*-diethoxymethyl derivative of acyclic amides and more particularly on *N*-benzyl-*N*-diethoxymethylacetamide **96**.

The preparation of the required reagent appeared to be much less efficient giving a poor yield of the desired carbenoid precursor (Scheme 80). This can be explained by the increased C=N double bond character of the amide resulting in a decrease of the nucleophilicity of the nitrogen atom.



Scheme 80

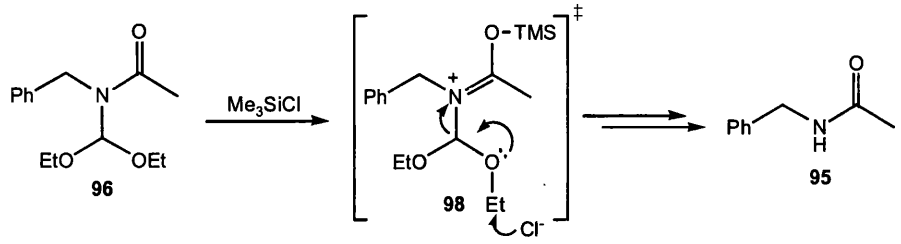
When the reaction was carried out with allylbenzene, under standard experimental conditions, cyclopropane products were obtained in low yield (Scheme 81).



Scheme 81

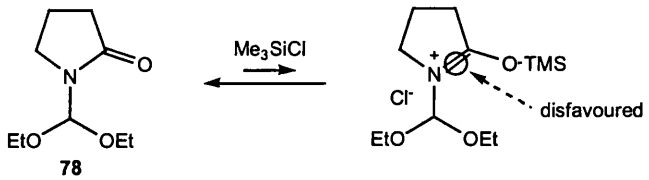
On examining the ^{1}H NMR of the crude reaction mixture, the principal component of the reaction was the starting amide **95**. This observation may indicate, as implied in

Scheme 82, that competitive silylation on oxygen provides a facile pathway for elimination of ethyl formate *via* **98**.



Scheme 82

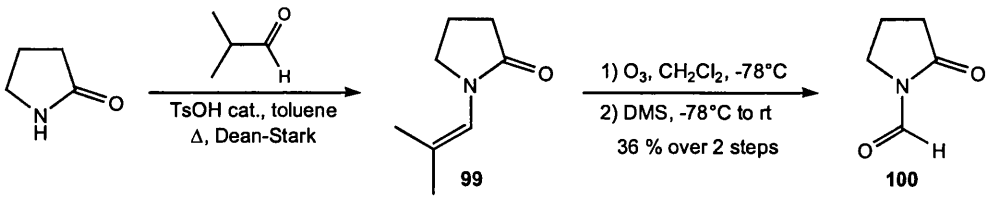
The formation of an analogous intermediate from the cyclic derivative **78** is of course less favourable on the grounds of ring strain (Scheme 83).



Scheme 83

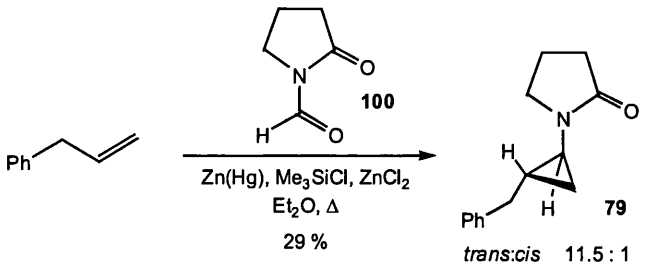
2.6.1 Study of the amidocyclopropanation reaction using *N*-formyl amides as the carbenoid precursor

As organozinc carbenoids can be generated from carbonyl compounds (*vide supra*), we decided to evaluate the cyclopropanating ability of *N*-formyl amides. Logically, we initially turned our attention to the study of *N*-formyl-2-pyrrolidinone **100** whose synthesis was performed in two straightforward steps with, as the key step, the ozonolysis of the enamide **99** (Scheme 84).



Scheme 84

Under standard conditions, the reaction between allylbenzene and **100** did yield the expected cyclopropanes but in a much lower yield than when the corresponding acetal derivative **78** was employed (entry 1 in Table 3) (Scheme 85). Attempts to improve the yield of this reaction using more powerful silicon electrophiles, such as trimethylsilyl triflate or 1,2-bis (chlorodimethylsilyl) ethane **62**, were fruitless.



Scheme 85

Very interestingly, this experiment provides strong presumptive evidence that the generation of the carbenoid species employing the *N*-diethoxymethyl amide **78** does not involve initial formation of its *N*-formyl derivative.

2.7 Studies toward the preparation of primary aminocyclopropanes

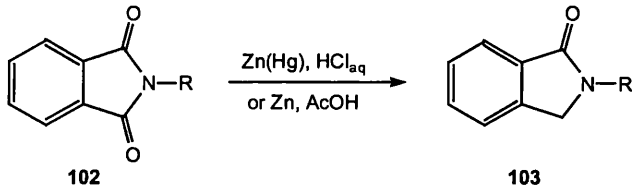
The discovery that organozinc carbenoids can be efficiently generated from an *N*-diethoxymethyl moiety attached to a simple cyclic amide was for us a significant breakthrough. In order to broaden the synthetic utility of this novel amidocyclopropanation reaction, we decided to focus our attention on the design of carbenoid precursors which could easily lead to free aminocyclopropanes. The preliminary studies undertaken with cyclic and acyclic amides indicated that the nitrogen functionality of such entities should preferably be incorporated into a cyclic structure in the first instance.

2.7.1 Study of the cyclopropanation reaction using *N*-diethoxymethyl phthalimide as the carbenoid precursor

Amongst the cyclic amino derivatives known for facile liberation of free amines, imides, such as phthalimide, are certainly those which have been the most frequently

used in organic chemistry.[96] Consequently, the synthesis of aminocyclopropanes from *N*-diethoxymethyl phthalimide **101** was investigated.

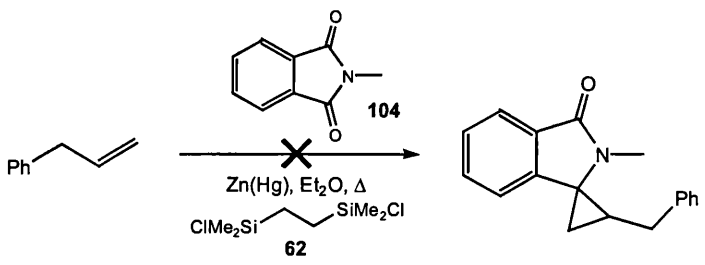
N-diethoxymethyl phthalimide **101** was prepared following the same procedure employed for the preparation of *N*-diethoxymethyl-2-pyrrolidinone **78** and was obtained in 63 % yield. Regrettably, the reaction between **101** and allylbenzene gave a complex mixture of products (as observed by NMR) which could be explained either by the instability of the carbenoid precursor **101** or the cyclopropanated product if it was formed, under the experimental conditions employed. Reduction of the phthalimide derivative could also have occurred and, indeed, *N*-alkylphthalimides of type **102** are known to be reduced to phthalimidines **103** in the presence of zinc in an acidic medium (Scheme 86).[97]



102 **103**

Scheme 86

As the reduction of the carbonyl group of **102** may also involve the generation of an organozinc carbenoid, we were curious to investigate if an alkene would be able to trap such a species. In consequence, the cyclopropanation reaction of allylbenzene with *N*-methylphthalimide **104** in the presence of zinc amalgam and the bis-silicon electrophile **62** was attempted. However, this reaction produced no cyclopropanes amongst the complex mixture of different products obtained (Scheme 87).



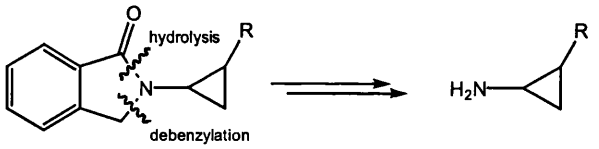
Scheme 87

Because *N*-alkylsuccinimides are generally not prone to such reduction, it was then envisaged to study the behaviour of the carbenoid species generated from *N*-diethoxymethyl succinimide.[97] The synthesis of this carbenoid precursor was attempted using different experimental procedures (reaction of succinimide with triethyl orthoformate or diethyl phenyl orthoformate in the presence or not of $AlCl_3$ at 150°C), but furnished only minute quantities of the desired product.

These discouraging results prompted us to study alternative carbenoid precursors.

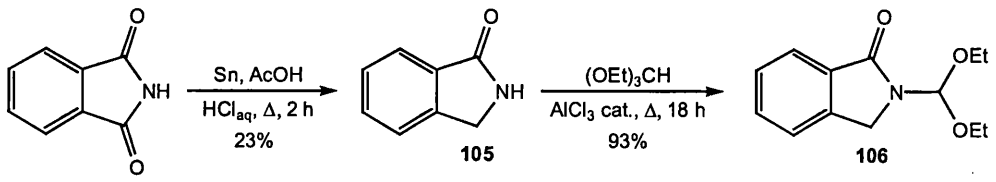
2.7.2 Study of the preparation of primary aminocyclopropanes using *N*-diethoxymethyl-2,3-dihydro-1-isoindolinone as the carbenoid precursor

The 2,3-dihydro-1-isoindolinone moiety is another substrate likely to lead to a primary amine. The cleavage of this auxiliary was expected to be achieved by catalytic hydrogenation and subsequent hydrolysis of the resulting secondary amide (Scheme 88).



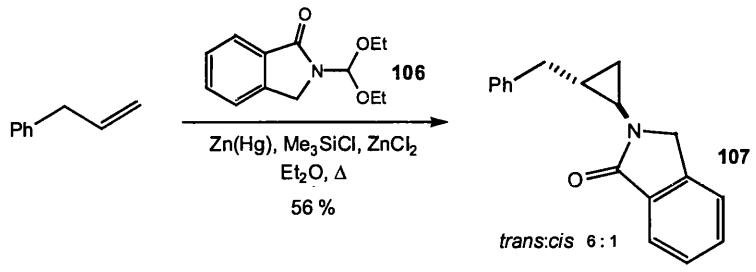
Scheme 88

As depicted in the following Scheme 89, the reduction of phthalimide with tin in an acidic medium, followed by the reaction of the intermediate amide with triethylorthoformate yielded the required *N*-diethoxymethyl-2,3-dihydro-1-isoindolinone **106** in a straightforward manner (Scheme 89).



Scheme 89

Pleasingly, the amidocyclopropanation reaction with this novel carbenoid precursor proved successful and gave the expected cyclopropanes **107** (Scheme 90).



Scheme 90

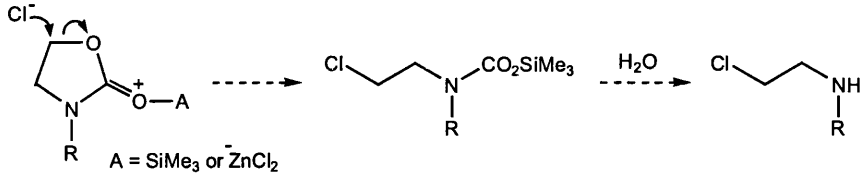
We subsequently investigated the stepwise deprotection of the amine functionality. Unfortunately all attempts to debenzylate **107** by catalytic hydrogenation failed and led to the complete recovery of the starting material.

Although alternative methods or routes to cleave the present auxiliary could have been attempted, a more promising candidate, developed simultaneously with **106**, received all our attention and consequently the study involving this carbenoid precursor was not further pursued.

2.7.3 Preliminary study of the use of *N*-diethoxymethyl oxazolidinones as carbenoid precursors

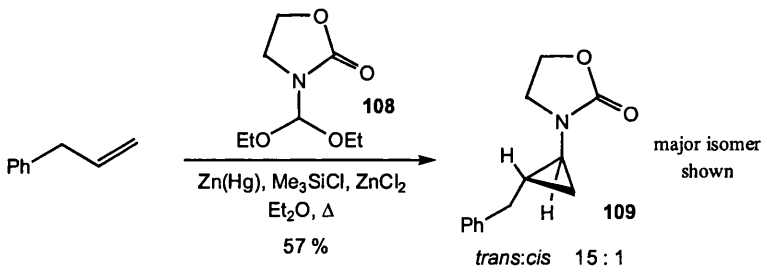
The focus of our research turned towards an alternative carbenoid precursor, *N*-diethoxymethyl-4,5-diphenyloxazolidinone **113**. This compound appeared to be a very attractive one to develop our methodology. Firstly, deprotection of the amino functionality can be performed in a single step by catalytic hydrogenation. Secondly, both enantiomers of **113** should be easily accessible and their use could lead to the preparation of chiral primary cyclopropylamines. Finally, 4,5-diphenyloxazolidinone derivatives are usually highly crystalline products, making their handling and purification simpler.[98]

As iodotrimethylsilane has been known to initiate the ring opening of an oxazolidinone, we were concerned that, during the cyclopropanation step, chlorotrimethylsilane in combination with $ZnCl_2$, a powerful Lewis acid, might behave in a similar manner (Scheme 91).[99]



Scheme 91

As a model reaction, we therefore investigated the cyclopropanation of allylbenzene with the simple *N*-diethoxymethyloxazolidinone **108**, which was prepared in 67 % yield using the standard conditions, and were pleased to note that the cyclopropanation reaction proceeded in 57 % yield without production of any ring-opened by-products (Scheme 92).

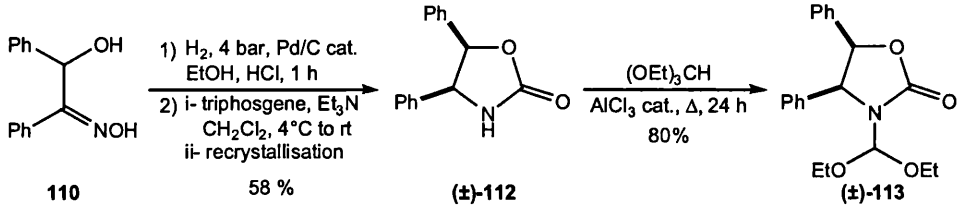


Scheme 92

Encouraged by this result, we then decided to evaluate the ability of *N*-diethoxymethyl-4,5-diphenyloxazolidinone **113** to yield aminocyclopropanes. Initially we planned to conduct this study using **(±)-113** in its racemic form.

The synthesis of **(±)-113** was achieved in three steps from α-benzoin oxime **110** (Scheme 93). The first step consisted of the hydrogenation of **110** at 4 bar in the presence of a catalytic amount of palladium on charcoal (Pd/C) in an acidic medium where two reactions occurred successively: the C=N oxime bond of **110** was initially

hydrogenated followed by cleavage of the N-O bond of the resulting hydroxylamine. In contrast to the results reported in the literature,[100] the hydrogenation of the oxime bond was not completely stereoselective and gave rise to a 93:7 mixture of *erythro* and *threo* amino alcohols **111**. This mixture was then reacted with triphosgene in the presence of triethylamine to furnish, after recrystallisation, pure *cis*-4,5-diphenyloxazolidinone **(±)-112**. Finally, this oxazolidinone was treated with triethylorthoformate in the presence of a catalytic quantity of aluminium chloride to yield the desired product **(±)-113** in 80 % yield. The compound is crystalline and can be stored for long periods of time in a desiccator. It has been noticed that the acetal moiety of **(±)-113**, and other *N*-diethoxymethyl compounds presented in this thesis, was partially hydrolysed in $CDCl_3$ depending on its source and manufacturer, therefore the use of DMSO-d_6 is preferable as the NMR solvent for these compounds.

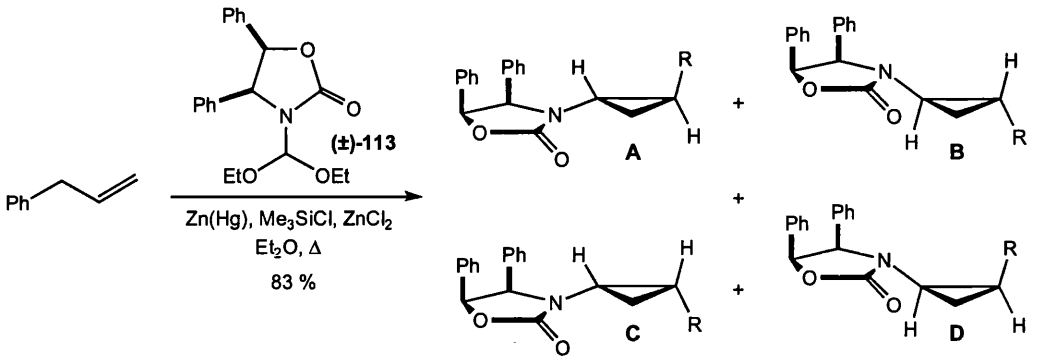


110 **(±)-112** **(±)-113**

Scheme 93

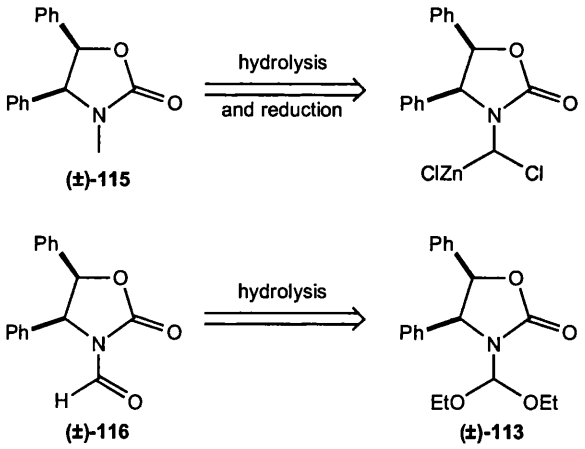
The procedure followed in the preliminary cyclopropanation using **(±)-113** varied from that used previously. The first significant difference was the use of dichloromethane to prepare the solution of carbenoid precursor, due to its insolubility in diethyl ether, and the second factor was the number of equivalents of carbenoid precursor employed relative to the alkene, being reduced from 2 to 1.5. Thus the conditions followed for the cyclopropanation reaction of allylbenzene involved the slow addition of **(±)-113** (1.5 eq) in dichloromethane to a suspension of zinc amalgam (15 eq), chlorotrimethylsilane (7.5 eq), $ZnCl_2$ (1.5 eq) and allylbenzene (1 eq) in diethyl ether at reflux.

The expected cyclopropanes **(±)-114** were obtained in 83 % yield as a 84:12:<2:<2 mixture of isomers A, B, C and D as depicted in the following Scheme 94 (with R=$PhCH_2$).



Scheme 94

As well as the cyclopropane products, degradation by-products of **(±)-113** were also observed. Traces of (±)-4,5-diphenyloxazolidinone (*vide supra*) and small quantities of 4,5-diphenyl-*N*-methyl-oxazolidinone **(±)-115** and 4,5-diphenyl-*N*-formyl-oxazolidinone **(±)-116** were also formed. **(±)-115** could be derived from the hydrolysis and reduction of the organozinc carbenoid and **(±)-116** from hydrolysis of the acetal moiety (Scheme 95). However their formation would imply that water was present in the reaction mixture, even though extra care was taken to exclude any traces of it.



Scheme 95

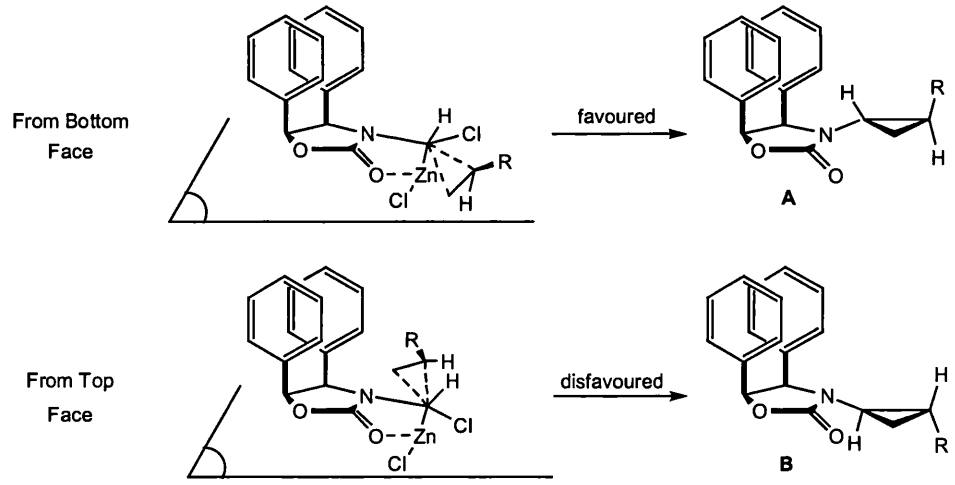
The production of these by-products could become problematic if they interfere with the isolation of the products, and this indeed was the case in the present instance, as the cyclopropane products **(±)-114**, purified by chromatography column, were contaminated with approximately 10 % by weight of 4,5-diphenyl-*N*-formyl-oxazolidinone **(±)-116** as

determined by ^{1}H NMR. Fortunately however, for the other cyclopropanes synthesised using **113**, no such problem was encountered (*vide infra*).

2.7.4 A proposed mechanism to account for the observed stereochemistry

It was of course of considerable interest to rationalise the observed stereochemical outcome in terms of a model which might ultimately lead to predictive power. Our initial ideas are developed in Scheme 96.

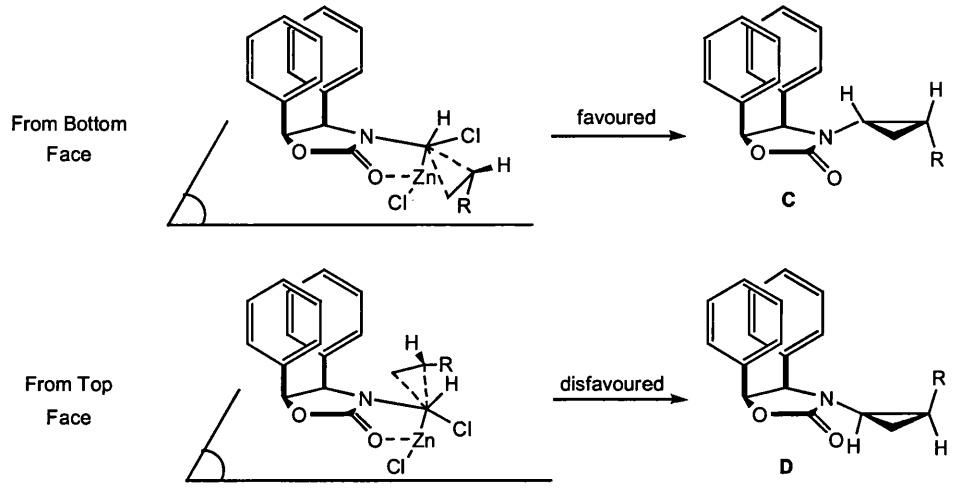
Thus, the oxazolidinone ring and the ring including the carbenoid centre and linked by the chelation between the zinc atom and the oxygen atom of the carbonyl group are firstly considered to be in the same plane. During the cyclopropanation reaction the alkene can then either approach from the bottom or the top face of this plane. As the top face is more hindered by the presence of the two phenyl rings, the alkene would consequently approach from beneath the plane and thus lead to the predominate formation of isomer A over B (Scheme 96 with R = CH_2Ph).



Scheme 96

X-Ray analysis of the major isomer obtained from a similar cyclopropanation reaction has confirmed the stereochemistry given for isomer A (*vide infra*). Attempts to determine the isomers structure by NMR, for example by looking for the presence or not of an interaction between the cyclopropylic protons in *beta* of the nitrogen atom and the aromatic rings of the oxazolidinone, failed.

A similar mechanism can be speculated for the *cis* isomers and account for the structures given for isomers C and D (Scheme 97).



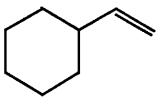
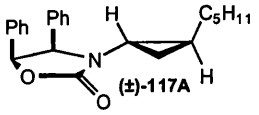
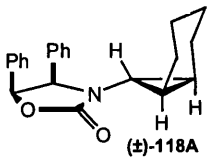
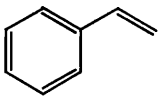
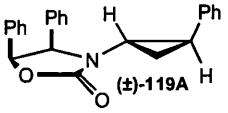
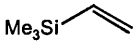
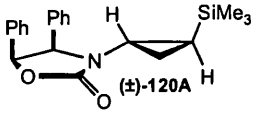
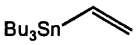
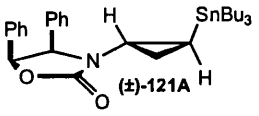
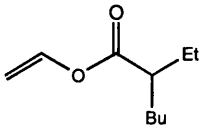
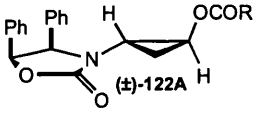
Scheme 97

2.7.5 Scope of the cyclopropanation reaction using (±)-*N*-diethoxymethyl-4,5-diphenyloxazolidinone

The scope of the cyclopropanation reaction using *N*-diethoxymethyl-4,5-diphenyloxazolidinone **(±)-113** was then investigated using a range of alkenes as shown in Table 5.

Two experimental procedures were followed, one using a slight excess of the carbenoid precursor relative to the alkene (method A) and, for selected alkenes, the alternative of employing an excess of alkene (method B). In each case, the major isomer was isolated as a pure product after careful chromatography. Pleasingly, the zinc amalgam did not form either soft balls or gum during these reactions.

The typical experimental procedure involved the addition of a solution of *N*-diethoxymethyl-4,5-diphenyloxazolidinone **(±)-113** (method A: 1.25 eq; method B: 1 eq) in dichloromethane over 6 hours to a suspension of vigorously stirred zinc amalgam (method A: 12.5 eq; method B: 10 eq), chlorotrimethylsilane (method A: 6.25 eq; method B: 5 eq), $ZnCl_2$ (method A: 1.25 eq; method B: 1 eq) and an alkene (method A: 1 eq; method B: 4 eq) in diethyl ether at reflux with further reaction for 16 hours.

	Alkene	Product	Isomer ratio[a] A:B:C:D	Method	Overall yield[b]	Yield of isomer A
1		 (±)-117A	88:8:<2:<2	A B	74 % 52 %	66 % 44 %
2		 (±)-118A	90:<2:6:<2	A B	58 % 49 %	54 % 46 %
4		 (±)-119A	56:6:28:6	A	55 %[c]	31 %
5		 (±)-120A	94:<2:<2:<2	A B	59 % 48 %	51 % 48 %
6		 (±)-121A	94:<2:<2:<2	A	24 %	22 %
7[d]		 (±)-122A	64:10:13:13	A	65 %	43 %

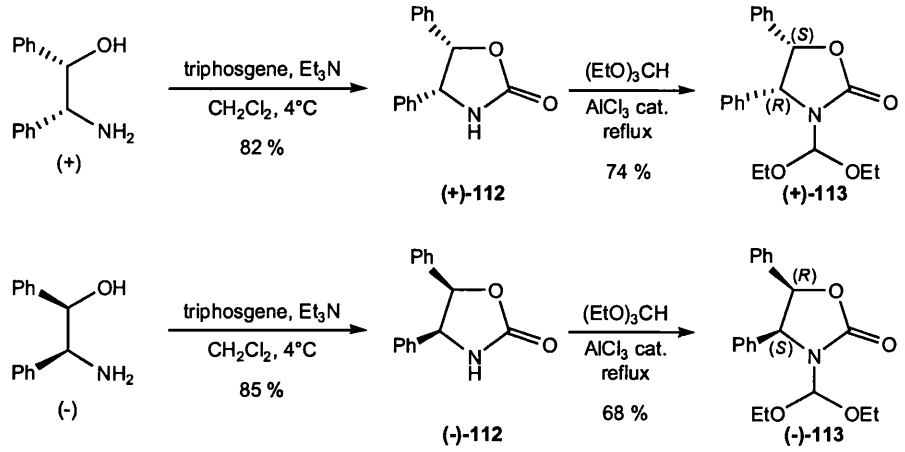
[a] Determined using ^{1}H NMR spectroscopy. [b] Overall yield refers to the total isolated yield of all isomers. [c] Traces of 4,5-diphenyl-*N*-formyl-oxazolidinone (±)-**116** were isolated with the products. [d] Addition of (±)-**113** over 2.5 hours. For convenience, only the major isomer is shown.

Table 5

From this study, it appears that both procedures give moderate to good yields of cyclopropanes (entries 1-5 and 7), although method A, involving the use of an excess of carbenoid precursor, was slightly more efficient (entries 1,2 and 4). A preference for the formation of isomer A (Scheme 96) was observed for all the substrates studied (entries 1-7), and in some cases almost no other isomers could be detected (entries 5 and 6). In entry 6, the instability of tributyl(vinyl)tin under the experimental conditions could account for the low yield obtained. This result was particularly disappointing as this substrate would have made an interesting precursor for further chemistry (*vide infra*).[101]

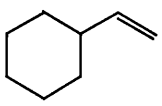
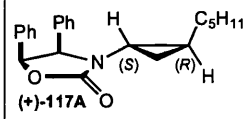
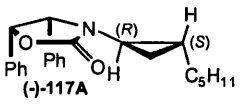
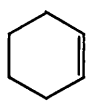
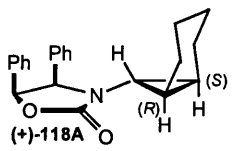
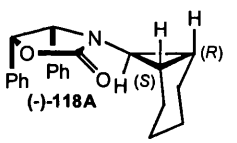
2.7.6 Synthesis of chiral cyclopropane derivatives

As both enantiomers, **(+)-113** and **(-)-113**, could be easily prepared from commercially available (+)- and (-)-2-amino-1,2-diphenylethanol (Scheme 98), the extension of the methodology developed became straightforward for the synthesis of optically active aminocyclopropanes.[102]



Scheme 98

Under similar conditions as those used with **(±)-113**, the cyclopropanation of vinyl cyclohexane and cyclohexene were performed with both chiral carbenoid precursors and were of comparable efficiency (Table 6).

	Alkene	Product using (+)-113	Overall yield (yield of A)	Product using (-)-113	Overall yield (yield of A)
1		 (+)-117A	63 % (56 %)	 (-)-117A	57 % (50 %)
2		 (+)-118A	61 % (53 %)	 (-)-118A	58 % (51 %)

For convenience, only the major isomer is shown.

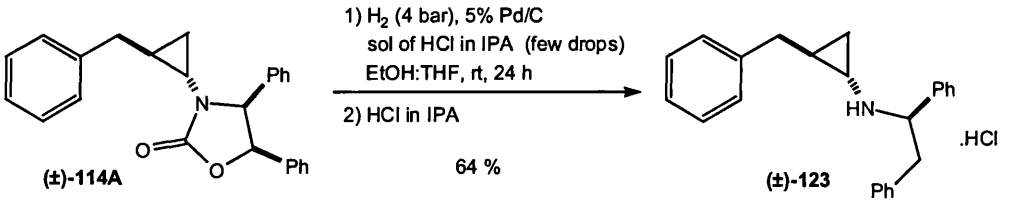
Table 6

The determination of the absolute configuration of these compounds was extrapolated from the absolute configuration established by an X-Ray crystallographic analysis of one of the cyclopropane derivatives prepared in a similar way using **(+)-113** (*vide infra*). Concurrently with the study of these cyclopropanation reactions, the conditions for the deprotection of the derived products were also under investigation.

2.7.7 Deprotection of 4,5-diphenyloxazolidinone cyclopropanes

Preliminary studies for the deprotection of (±)-4,5-diphenyloxazolidinone cyclopropanes were carried out using **(±)-114A**.

The hydrogenolysis of **(±)-114A** appeared to be very dependent on the catalyst and conditions employed. Hydrogenation for 24 hours at 4 bar using 5% Pd/C as the catalyst in an acidic medium achieved only partial deprotection yielding (±)-**123** as the only product isolated after work-up (Scheme 99).



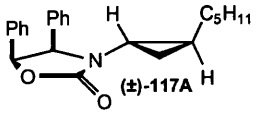
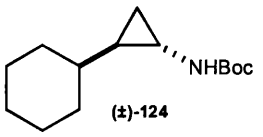
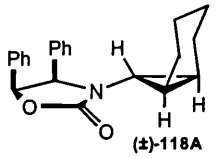
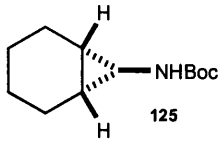
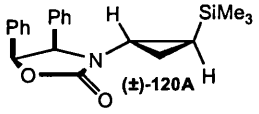
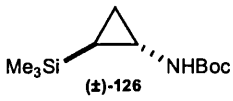
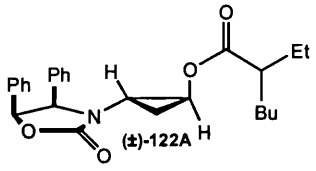
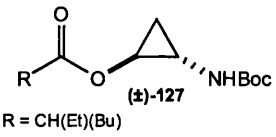
Scheme 99

Transfer hydrogenation using ammonium formate and the same catalyst was also attempted and led unsatisfactorily to a mixture of products.

Pleasingly, complete cleavage of the oxazolidinone ring was obtained using Pearlman's catalyst (20 % $Pd(OH)_2/C$) in a mixture of THF:AcOH at 4 bar. However, isolation of the resultant pure free primary amine was difficult. In order to overcome this problem, we decided that the amino function would be protected, as the Boc derivative, prior to its purification.

The protection of the amine was performed by treating the crude reaction mixture after hydrogenation with Boc_2O in the presence of an excess of triethylamine in CH_2Cl_2. The desired carbamate was then easily purified by chromatography on silica gel.

This procedure was applied to the deprotection of the following racemic cyclopropane derivatives (Table 7).

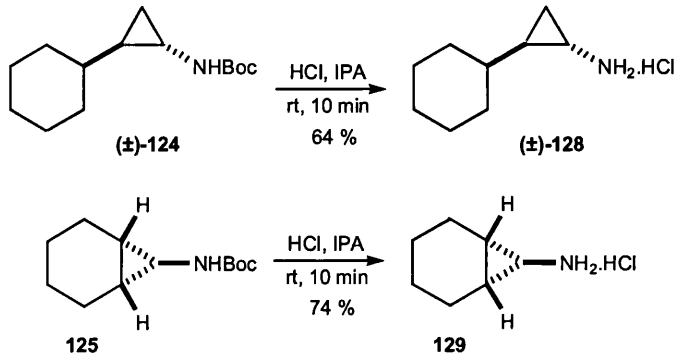
	Substrate	Product	Time of hydrogenation	Overall yield
1	 (±)-117A	 (±)-124	12 h	64 %
2	 (±)-118A	 125	17 h	58 %
3	 (±)-120A	 (±)-126	13 h	22 %
4	 (±)-122A	 (±)-127 R = CH(Et)(Bu)	11.5 h	~15 %[a]

[a] Trace of an unidentified by-product was isolated with the product.

Table 7

From table 7, the two step procedure was particularly effective for the first two substrates (entries 1 and 2), whereas, with the trimethylsilyl substituted cyclopropane, the overall yield of carbamate formation was low (entry 3). This may have resulted from the partial loss of the somewhat volatile intermediate amine during work up, as the crude reaction mixture was concentrated at high temperature *in vacuo* in order to remove the acetic acid which was used as solvent. However this problem was avoided by performing the hydrogenation under different conditions and by using a 'heavier' silyl group (*vide infra*). From entry 4, the presence of an ester group was clearly not well tolerated under the acidic conditions employed for the hydrogenation step, since numerous by-products were formed leading to a very low overall yield of the desired product (entry 4).

As expected the deprotection of the Boc protecting group of **(±)-124** and **125** was easily achieved using a solution of hydrochloric acid in isopropanol thereby affording the aminocyclopropanes as their hydrochloride salts (Scheme 100).



Scheme 100

As the overall efficiency of the two-step protocol developed for the preparation of the Boc protected amines was not completely satisfactory, an alternative approach was investigated. This latter consisted in performing the two steps in one, in other words, carrying out the hydrogenolysis of the oxazolidinone ring in the presence of Boc_2O in order to obtain the protected amines directly. To our delight, when this approach was applied to the deprotection of the set of chiral oxazolidinones previously studied (*vide supra*), excellent yields of the carbamates were consistently obtained (Table 8). The deprotection of **(+)-** and **(-)-118A** furnishes, of course, the same *meso* compound **125**.
The general procedure involved the hydrogenation of the substrate in the presence of Pearlman's catalyst and Boc_2O (2 eq) in THF at 5.5-6 bar and at 30-35°C. However, these conditions have not been fully optimised.

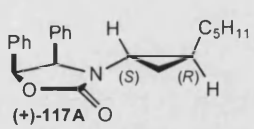
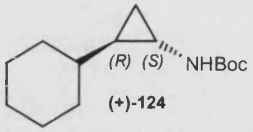
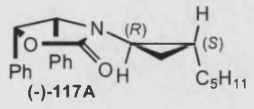
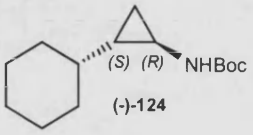
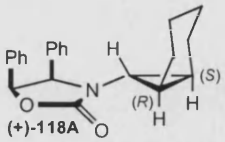
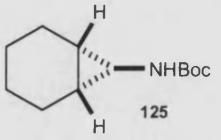
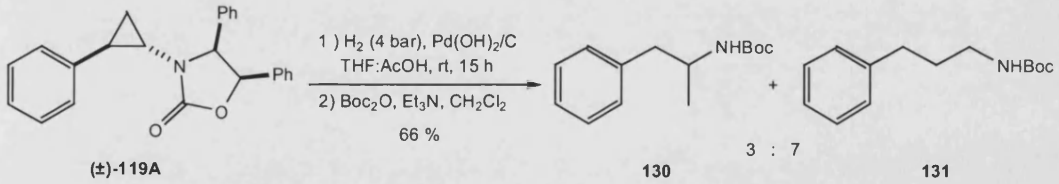
	Substrate	Product	Experimental conditions	yield
1	 (+)-117A	 (+)-124	5.5 bar / 7 h / 30°C	95 %
2	 (-)-117A	 (-)-124	5.5 bar / 8 h / 30°C	93 %
3	 (+)-118A	 125	6 bar / 8 h / 35°C	95 %

Table 8

Some limitations of these deprotection procedures were nevertheless highlighted when substrates possessing a phenyl ring adjacent to the cyclopropyl unit were used. Indeed, the cyclopropane of **(±)-119A** was found to undergo ring opening during the hydrogenation step and to yield a mixture of carbamates **130** and **131** (Scheme 101). This feature appears to be an inherent problem with α-arylcyclopropyl compounds.[40]



(±)-119A 130 131

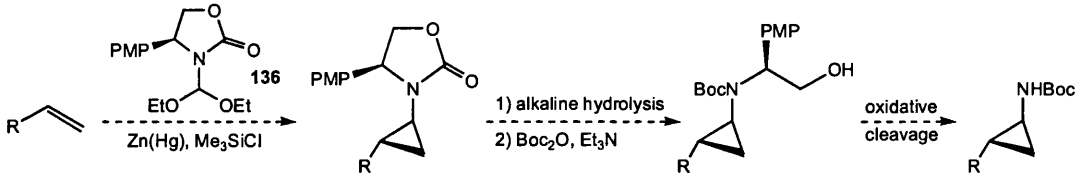
Scheme 101

Hence, in order to obtain the corresponding primary phenylcyclopropylamine, alternative methods such as the use of carbenoid precursors which would require different deprotection conditions or the development of other sequences for the deprotection of diphenyloxazolidinone derivatives were then considered.

2.7.8 Studies towards the preparation of primary arylcyclopropylamines

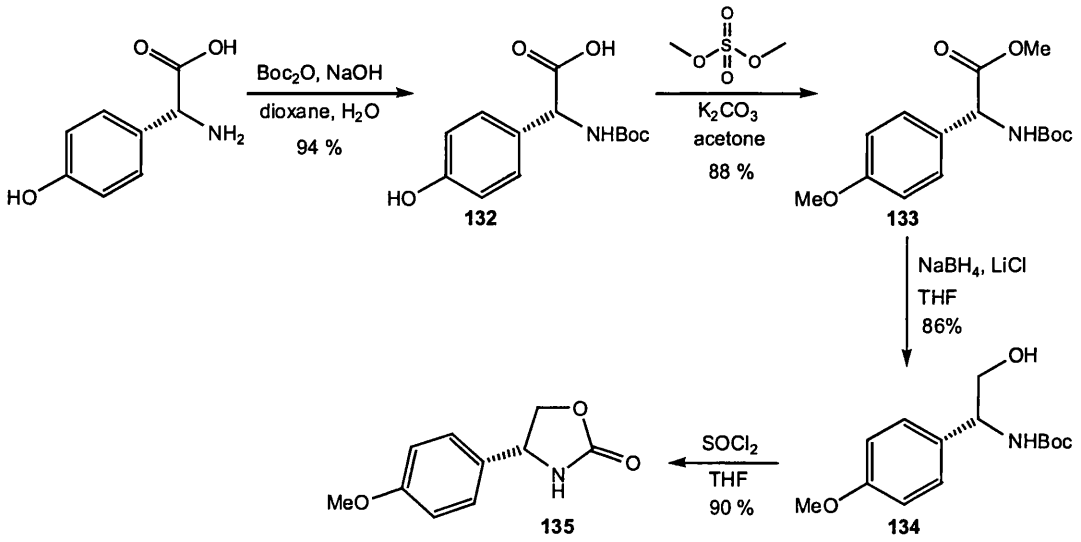
2.7.8.1 Use of a different carbenoid precursor

In order to overcome the problem raised by the hydrogenolysis of the cyclopropane ring observed with **(±)-119A**, we first considered employing a carbenoid precursor which would require a different procedure for its deprotection. For this purpose, we decided to study the reactivity and deprotection of the 4-(4-methoxyphenyl)-oxazolidin-2-one derivative **136**. This auxiliary was expected to be cleaved by alkaline hydrolysis and subsequent mild oxidative cleavage of the 4-methoxy benzyl group using for example cerium ammonium nitrate (Scheme 102).[103]



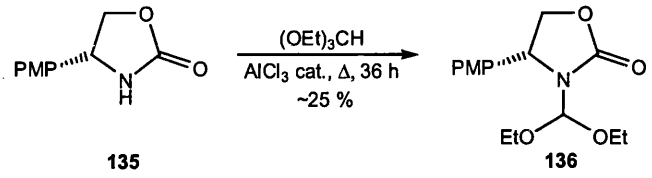
Scheme 102

4-(4-methoxyphenyl)-oxazolidin-2-one **135** was synthesised, on a multigram scale, in four straightforward steps from D-(4-hydroxyphenyl)-glycine in an overall yield of 64 % (Scheme 103). The key step of this sequence was the formation of the oxazolidinone ring by treating the Boc protected amino alcohol **134** with an excess of thionyl chloride.



Scheme 103

Disappointingly however, the treatment of **135** with triethyl orthoformate in the presence of a catalytic amount of $AlCl_3$ gave a mixture of products from which the *N*-diethoxymethyl derivative **136** could be isolated in only 25 % yield (Scheme 104).



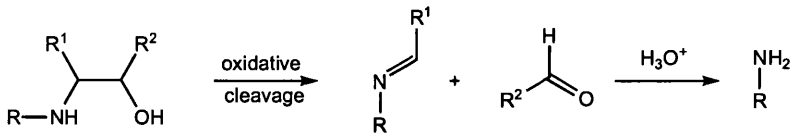
135 **136**

Scheme 104

This result prompted us to investigate a more general method for deprotection of oxazolidinone rings.

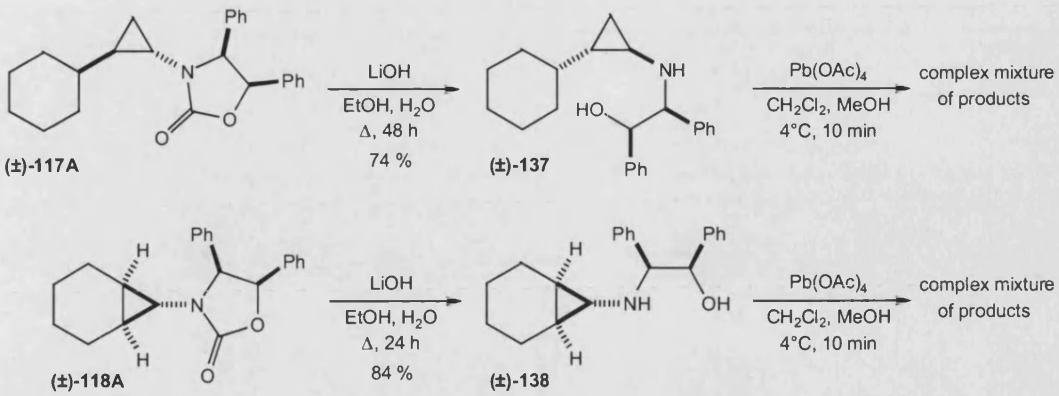
2.7.8.2 Studies of alternative methods for the cleavage of the diphenyloxazolidinone ring

We then reasoned that any vicinal amino alcohols could be cleaved by oxidation and thus lead to the free amine after hydrolysis of the intermediate imine (Scheme 105). This would allow us to employ the diphenyloxazolidinone derivatives whose chemistry has already been developed.



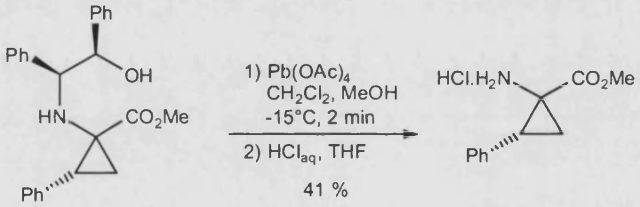
Scheme 105

The most common reagent used for such oxidations is lead tetraacetate, which is known to be compatible with the presence of a cyclopropane ring.[104] However, when this cleavage reaction was investigated using **(±)-137** and **(±)-138**, it was found that, in both cases, a complex mixture of products was produced (Scheme 106).



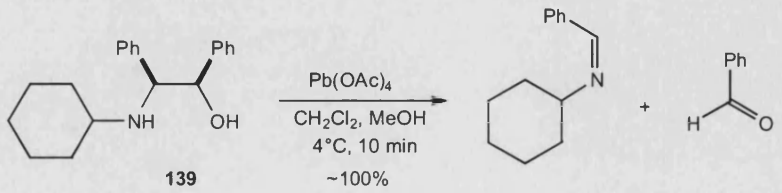
Scheme 106

From the literature, one similar reaction using lead tetraacetate required optimised conditions to finally give the expected product in a moderate yield (Scheme 107).[105]



Scheme 107

In complete contrast, when the reference product **139** was treated with lead tetraacetate the expected imine and benzaldehyde were obtained in almost quantitative yield (Scheme 108) showing clearly that the proximity of the cyclopropyl ring to the nitrogen atom is not well tolerated when lead tetraacetate is employed.



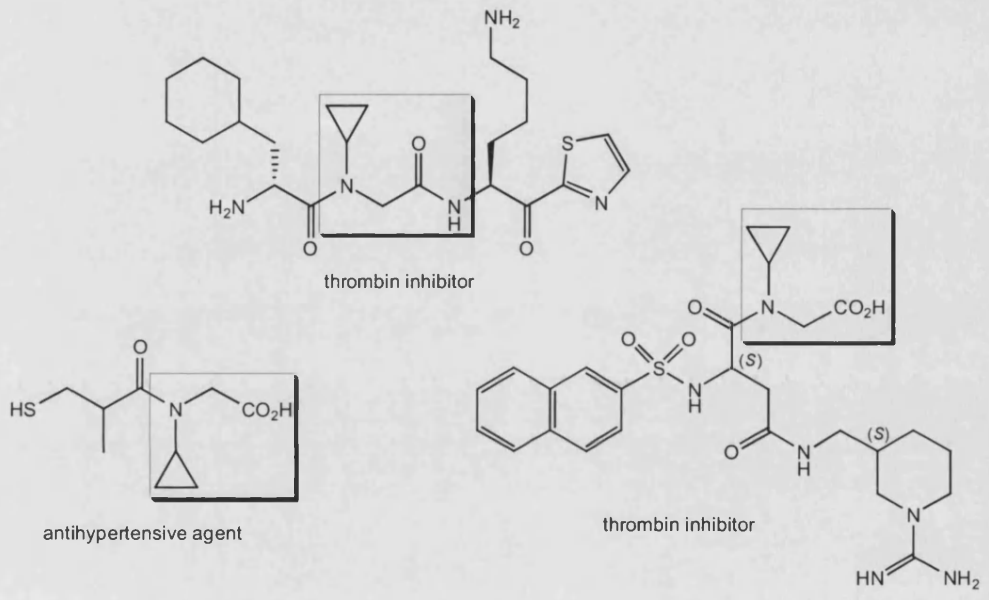
Scheme 108

Extensive work was then carried out to find conditions to achieve the efficient oxidative cleavage of amino alcohols using 'non metallic' oxidising reagents such as periodic acid, H_5IO_6, and sodium metaperiodate, $NaIO_4$.[106] The reference product **139** and the phenylcyclopropyl amino alcohol **(+)-140**, which was obtained in 70 % by hydrolysis of **(+)-119A** using $KOSiMe_3$ in THF at 60 °C, were both used in this study. Reactions involving either H_5IO_6 or $NaIO_4$ are generally performed in a mixture of alcohol and water. However our substrates were found to be rather insoluble in this medium and the oxidation reactions did not proceed satisfactorily. When supported on silica gel, $NaIO_4$ is effective in dichloromethane, a solvent in which our substrates are soluble.[107] Using this reagent, the reactions employing both substrates were complete in one hour as observed by TLC. However, after filtration, extensive washing of the filtered silica gel, and concentration of the reaction mixture, the recovered mass of the crude reaction mixture was curiously much lower than expected. A number of reactions using $NaIO_4$ in a mixture of THF or dichloromethane with various amounts of water were then carried out, however the results obtained were variable and not reproducible. This approach, which appeared at first to be promising, had therefore to be abandoned.

For the preparation of arylcyclopropylamines, a totally different strategy involving a palladium cross-coupling reaction was accordingly envisaged and is presented in section 2.9 (*vide infra*).

2.8 Studies on the synthesis of *N*-substituted cyclopropyl amino alcohols and acids

A number of *N*-cyclopropyl amino acids and their derivatives are present in molecules showing interesting biological activities although in general, no substituents are present on the cyclopropyl ring since simple aminicyclopropane is always selected as a building block (Scheme 109).[108]

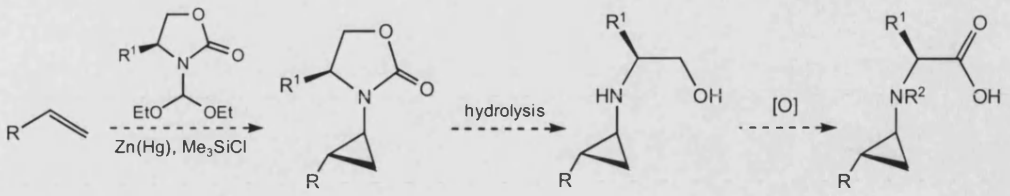


Scheme 109

To date, no methods which would lead easily to the preparation of *N*-substituted cyclopropyl amino acids have been reported, even although these compounds could be very valuable either for medicinal or peptide chemistry. Consequently, we elected to investigate the application of our newly developed methodology towards the synthesis of amino alcohols and acids possessing substituted cyclopropyl unit adjacent to the nitrogen atom

Initially we considered the cyclopropanation of alkenes with *N*-diethoxymethyl oxazolidinones derived from different amino acids. Subsequent hydrolysis of the oxazolidinone ring would then furnish amino alcohols and the *N*-substituted

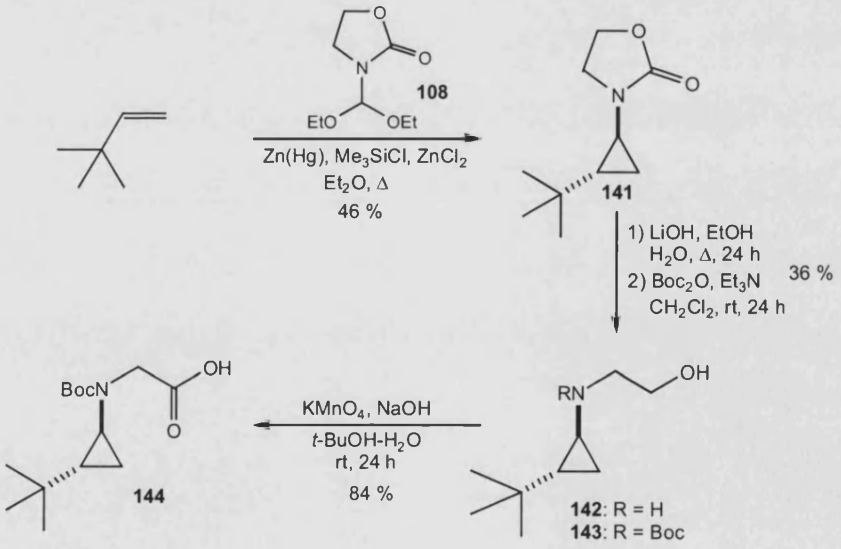
cyclopropyl amino acids would then be obtained by oxidation of their corresponding alcohols (Scheme 110).



Scheme 110

The feasibility of this approach was initially verified by the preparation of the *N*-substituted cyclopropyl glycine derivative **144**.

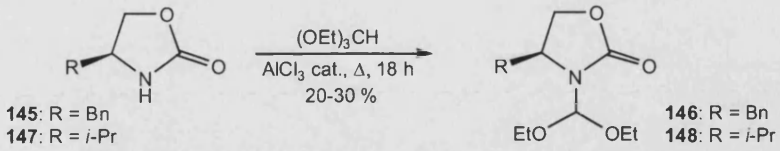
The synthesis, commencing with the cyclopropanation reaction between **108** and 3,3-dimethylbutene, proceeded with very good stereocontrol to yield almost exclusively the *trans* cyclopropane **141**. Hydrolysis of the oxazolidinone ring and subsequent protection of the resulting secondary amine gave the amino alcohol **143**, which was then oxidised very cleanly with potassium permanganate in alkaline medium to furnish the desired amino acid **144** (Scheme 111).



Scheme 111

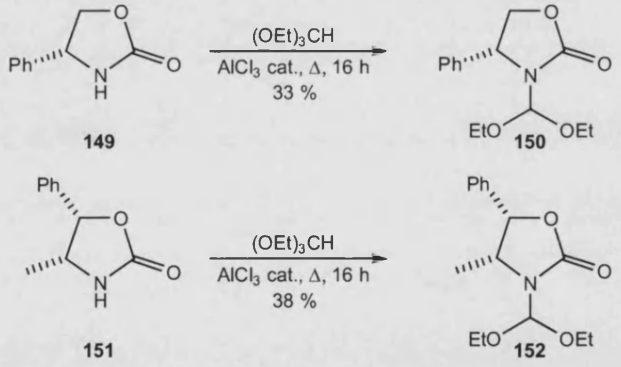
Encouraged by this result, we decided to attempt a similar sequence with different amino acids. Curiously however, when the oxazolidinones derived from phenylalanine

and valine were treated with triethyl orthoformate, a mixture of products was obtained and the desired products could only be isolated in poor yields (Scheme 112).



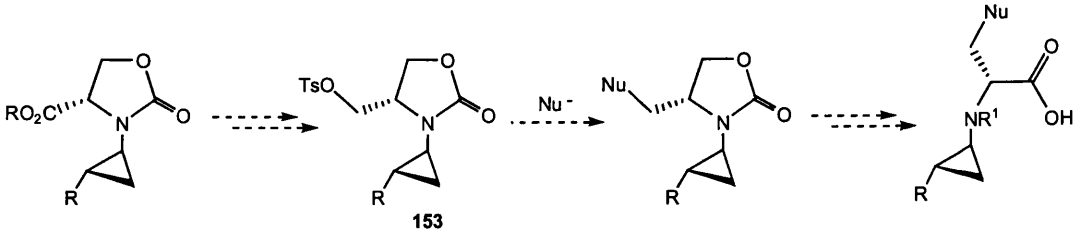
Scheme 112

As a comparison, under similar conditions, *N*-diethoxymethyloxazolidinone **108** and 4,5-diphenyloxazolidinone **113** were obtained in 67 % and 68-80 % yield respectively. In an attempt to rationalise this surprising substrate dependence, the same reaction was performed with compounds structurally similar to 4,5-diphenyloxazolidinone **112**, such as 4-phenyloxazolidinone **149** and 4-methyl-5-phenyloxazolidinone **151**, but once again, the yields for these transformations were low (Scheme 113). At present, we therefore have no logical rationalisation for the substituent dependence on the yields of these products.



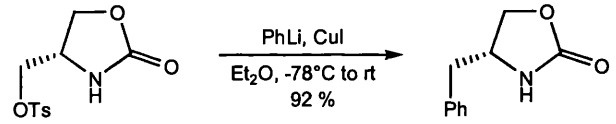
Scheme 113

As the carbenoid precursors in this series could not be obtained in good yields, we were led to consider an alternative sequence. Another strategy was therefore envisaged, starting from serine derivatives and preparing the tosylate **153** which could then react with nucleophiles (Scheme 114). This sequence appeared attractive as it would lead to the preparation of a wide range of products by varying the nucleophile employed.



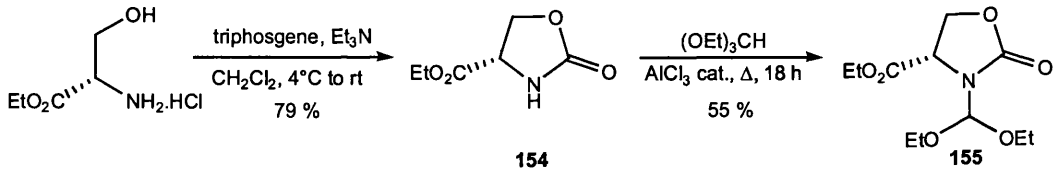
Scheme 114

In this respect, work by Sibi *et al.* was particularly informative. This group has shown that, with an unsubstituted oxazolidinone, the displacement of the tosylate group is achieved very effectively using cuprates (Scheme 115).[109]



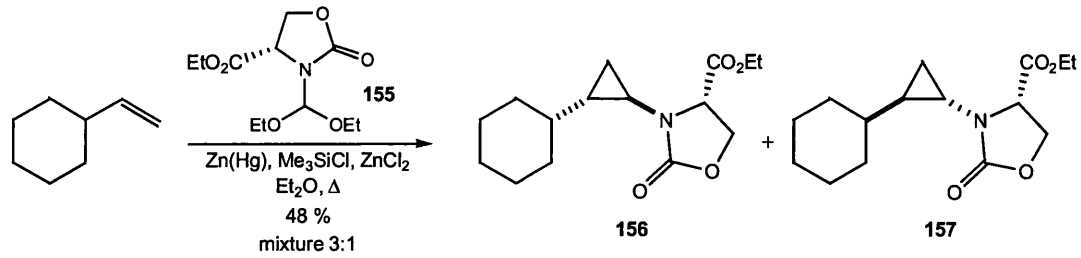
Scheme 115

The study of this novel route commenced with the preparation of **155** in two steps from L serine ethyl ester hydrochloride (Scheme 116). Using oxazolidinone **154**, the synthesis of the *N*-diethoxymethyl derivative was, in this case, obtained in a moderate but acceptable yield.



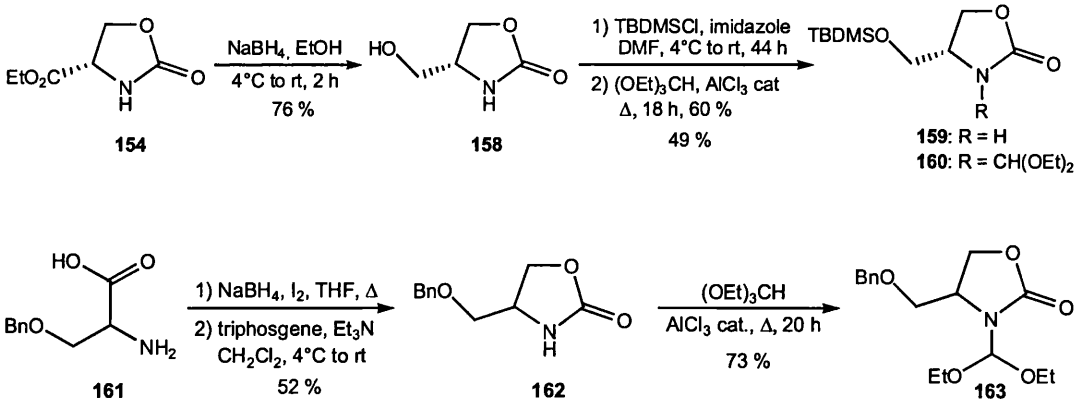
Scheme 116

The cyclopropanation reaction of vinyl cyclohexane with **155** was then carried out under standard conditions and gave predominantly a 3:1 inseparable mixture of the two *trans* diastereoisomers **156** and **157**, the major isomer was not identified (Scheme 117).



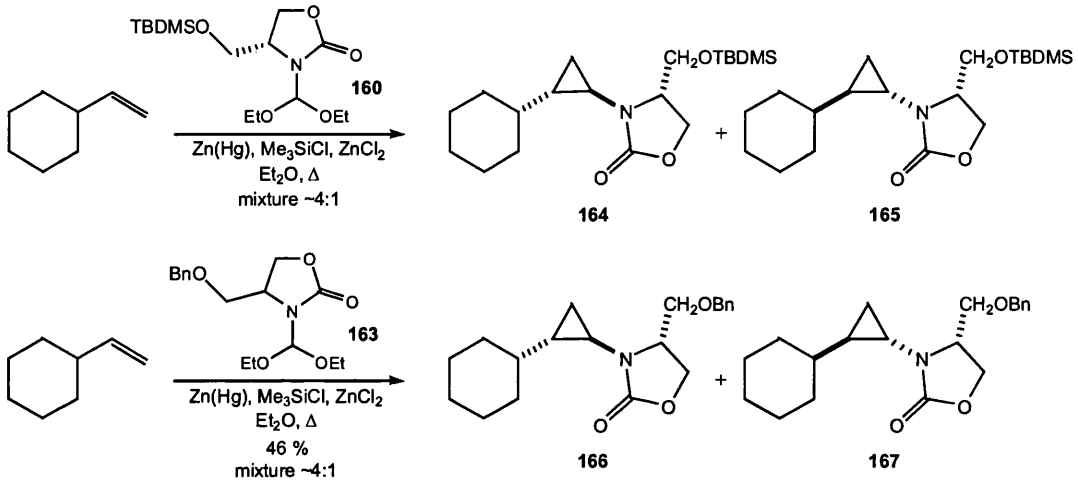
Scheme 117

We consequently reasoned that better stereocontrol of the cyclopropanation reaction might be achieved using a carbenoid precursor possessing a more hindered side chain. As the use of an excess of triethylorthoformate, in the presence of aluminium chloride, will transform any ester to the ethyl ester **155**, we had to turn our attention to carbenoid precursors possessing functional groups other than esters. The derivatives which would offer the most flexibility appeared to us to be the derived protected alcohols. We thus prepared the two alcohols **160** and **163** bearing a TBDMS and a benzyl group. **160** was synthesised in two steps from the alcohol **158** obtained by reduction of the ester moiety of **154** (Scheme 118). Treatment of **158** using sodium hydride and benzyl bromide was found to give mainly the *N*-benzylated product rather than the expected *O*-benzylated derivative due to the increased acidity of the N-H proton of the carbamate when incorporated into a cyclic structure. The route finally followed involved the use of the commercially available *O*-benzyl-DL-serine **161** and yielded the desired product **163** in three steps (Scheme 118).



Scheme 118

Cyclopropanation reactions were then performed with vinyl cyclohexane and gave for both carbenoid precursors **160** or **163** approximately a 4:1 mixture of the two *trans* diastereoisomers as determined by a study of the ^1H NMR of the crude reaction mixture; the major isomers for these reactions were not identified (Scheme 119). For the reaction involving **160**, no yield was calculated as the addition of the carbenoid precursor was interrupted at an early stage due to the formation of hard zinc balls.



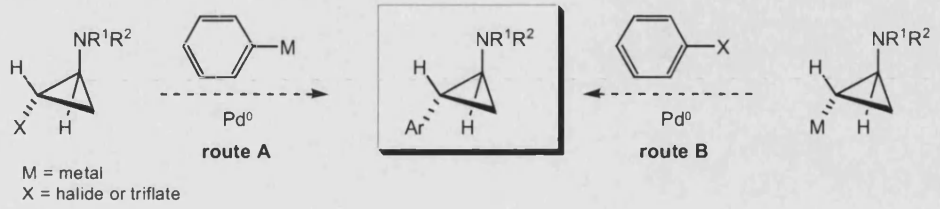
Scheme 119

These results demonstrated that the use of carbenoid precursors possessing a hindered side chain induced a certain degree of stereocontrol. In order to increase this stereocontrol, a wider range of protecting groups for the alcohol functionality should of course be screened. However, this study was not further developed because of time constraints.

2.9 Studies on the synthesis of arylcyclopropanes *via* a palladium-catalysed cross-coupling reaction

Although a range of free aminocyclopropanes was accessible by our newly developed method, the synthesis of primary arylcyclopropylamines still represented a challenge (*vide supra*). As a cyclopropyl ring adjacent to a phenyl group was found to be hydrogenolysed during the deprotection step, we considered introducing the aryl functionality at a later stage *via* a palladium-catalysed cross-coupling reaction. Two

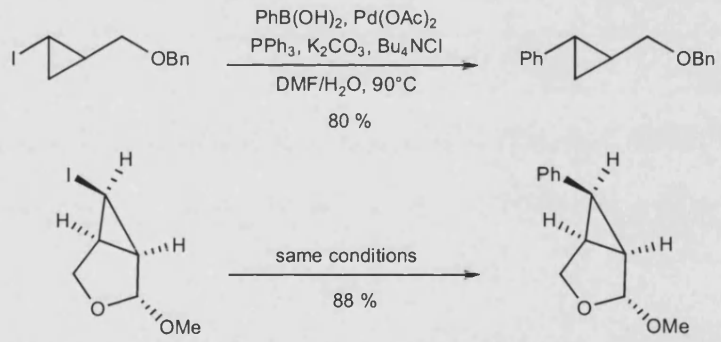
approaches were postulated for creation of a new cyclopropyl-aryl bond; either by reaction between a cyclopropyl halide and an aryl organometallic species (route A) or between an aryl halide or triflate and a cyclopropyl organometallic species (route B) (Scheme 120).



Scheme 120

2.9.1 Palladium-catalysed cross-coupling reactions involving cyclopropyl halides

The successful insertion of palladium (0) into a cyclopropyl iodide bond was first reported by Charette *et al.* and allowed the effective preparation of arylcyclopropanes *via* the Suzuki type cross-coupling reaction (Scheme 121).[110]



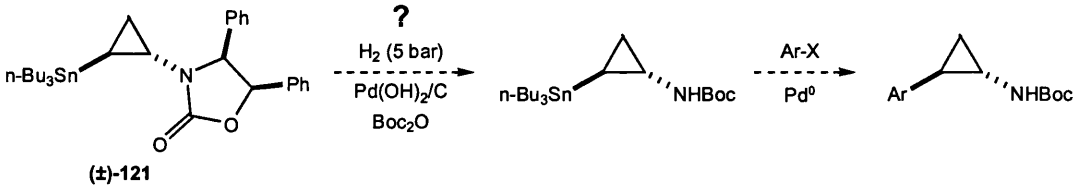
Scheme 121

However such an approach is not feasible using our methodology, as cyclopropyl iodides cannot be prepared under the reductive conditions employed for the cyclopropanation reaction.

2.9.2 Palladium-catalysed cross-coupling reactions involving cyclopropyl organometallic species

Cyclopropylzincs,[110c,111] -boronic acids,[110b,112] -boranes,[113] -borates[114] and -stannanes[101] have all been shown to undergo palladium-catalysed cross-coupling reactions with aryl halides and triflates to generally yield arylcyclopropane products in good yields.

We have previously reported the preparation of the cyclopropylstannane derivative **(±)-121** using our methodology. However, this compound was obtained in low yield due to the instability of tributyl(vinyl)tin under the cyclopropanation reaction conditions (*vide supra* 2.7.4). Furthermore, in order to achieve the synthesis of primary arylcyclopropanes, the carbon-tin bond would have to withstand hydrogenation at high pressure and this is unprecedented in the literature (Scheme 122).



Scheme 122

The preparation of free aminocyclopropanes using boron derivatives would also suffer from the same limitations. In addition, cyclopropylboron compounds have not been previously prepared employing an organozinc carbenoid generated by the zinc/chlorotrimethylsilane system and thus the reactivity of their alkenyl precursors would therefore have to be demonstrated.

At this stage, it was realised that none of the previously reported cyclopropyl organometallic species would be entirely appropriate for the cyclopropanation and/or hydrogenation steps of the sequence studied. As a consequence, the use of more robust substrates was investigated. Recently, organosilicon compounds have been shown to be competent coupling partners for palladium-catalysed cross-coupling reactions.[115] Under our standard cyclopropanation conditions, vinyl trimethylsilane was found to be cyclopropanated effectively to provide almost exclusively one isomer (*vide supra*).

Additionally, a carbon-silicon bond is not expected to be cleaved upon hydrogenation, making this class of compounds ideal to study using our methodology.

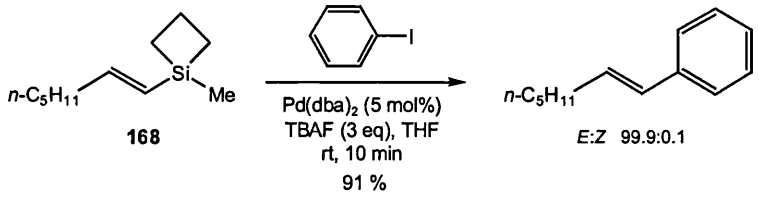
We therefore decided to investigate the ability of cyclopropylsilanes to undergo cross-coupling reactions. Although such transformations have been routinely performed with alkenyl, aryl and alkynyl organosilicon compounds, cyclopropylsilanes have, to date, not been utilised.

2.9.3 Palladium-catalysed cross-coupling reactions of organosilicon compounds

2.9.3.1 Background

Recently, the use of organosilicon compounds to create carbon-carbon bonds has received increased attention, especially due to the low toxicity, ready accessibility and high chemical stability of these reagents. Activated by a nucleophilic promoter, fluoro-, chloro-, alkoxy-, hydroxy- and alkylsilanes undergo palladium-catalysed cross-coupling reactions and usually provide the coupled products in very high yields under mild conditions.[115]

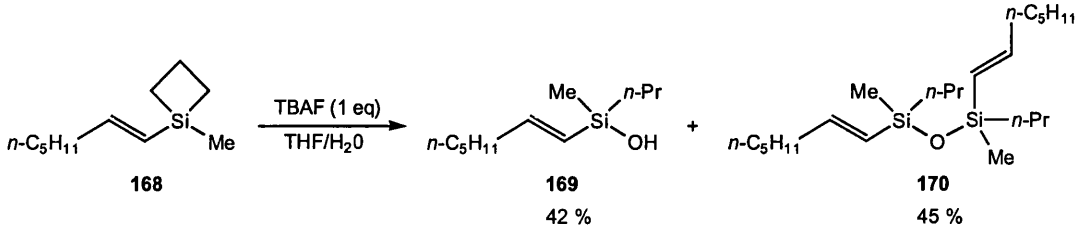
To avoid any complications during the cyclopropanation reaction, the use of an all-carbon silicon species was considered. The effective and general application of alkylsilanes in cross-coupling reactions was initially reported by Denmark. His pioneering work demonstrated that alkenylsilacyclobutanes, in the presence of TBAF and a catalytic amount of a palladium (0) source, underwent facile cross-coupling with aryl and vinyl iodides with excellent stereocontrol (Scheme 123).[116]



Scheme 123

The active species in the reaction described above were finally found to be the silanol **169** and the disiloxane **170** both of which were produced when the silacyclobutane **168**

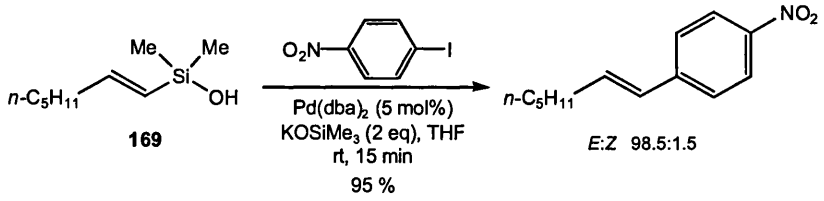
was treated with TBAF and water; water which is present in the commercial THF solution of TBAF employed (Scheme 124).[117]



168 → **169** 42 % + **170** 45 %

Scheme 124

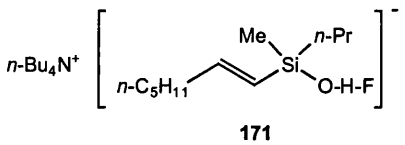
On the basis of these findings, the reactivity of silanols, siloxanes and silyl ethers were investigated and they were found to be very efficient coupling partners.[115,118] With silanols, effective couplings could be promoted with the use of a base, such as potassium trimethylsilanolate or cesium carbonate, instead of a fluoride source (Scheme 125).[119]



169 → *E*:*Z* 98.5:1.5

Scheme 125

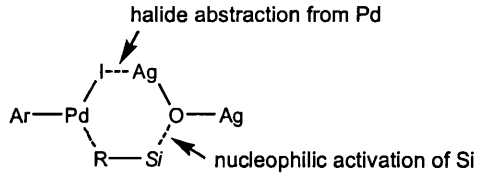
Recently, Denmark *et al.* undertook both NMR and kinetic studies to gain a better understanding of the mechanism of the fluoride promoted cross-coupling reaction and postulated that **171** could be an intermediate involved in the transmetallation step (Scheme 126).[120]



171

Scheme 126

In parallel with Denmark's work, Mori *et al.* demonstrated that, as an alternative, alkenyl- and arylsilanols could be activated with silver(I) oxide.[121] The silver atom was believed to promote halide atom abstraction from the arylpalladium iodide intermediate to form a more reactive cationic palladium species, while the oxygen atom reacted as a nucleophilic activator thus generating the silicate intermediate involved in the transmetallation (Scheme 127).



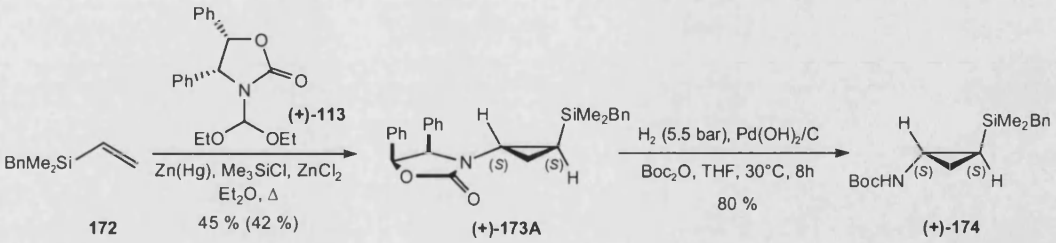
Scheme 127

2.9.3.2 A preliminary study towards the palladium-catalysed cross-coupling reactions of cyclopropylsilanes

As cyclopropanes are known to have some sp^2 character[122] and, when appropriately functionalised, to be successfully cross-coupled under Negishi, Suzuki and Stille conditions (*vide supra*), we were confident that cyclopropylsilanes would also act as coupling partners.

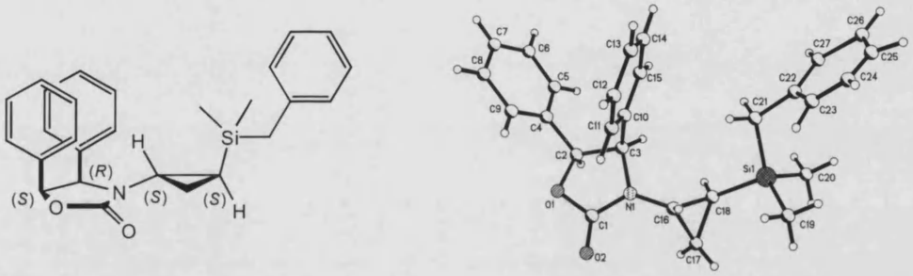
Amongst the different silyl groups involved in cross-coupling reactions, the benzyldimethylsilyl moiety appeared to be the most appropriate to study as it is a stable all-carbon silicon species which undergoes rapid debenzylation upon treatment with TBAF to yield its corresponding silanol, the active species involved in this type of cross-coupling reaction. Alkenyl benzyldimethylsilanes are also easily prepared.[123]

In a very encouraging initial experiment, we demonstrated that the benzyldimethylvinyl silane **172**, readily synthesised in 62% yield from the reaction of benzylmagnesium chloride and chlorodimethylvinylsilane, was stable under the experimental conditions used for the cyclopropanation/hydrogenation sequence and led to the formation of the desired vicinal amino cyclopropylsilane **(+)-174** (Scheme 128).



Scheme 128

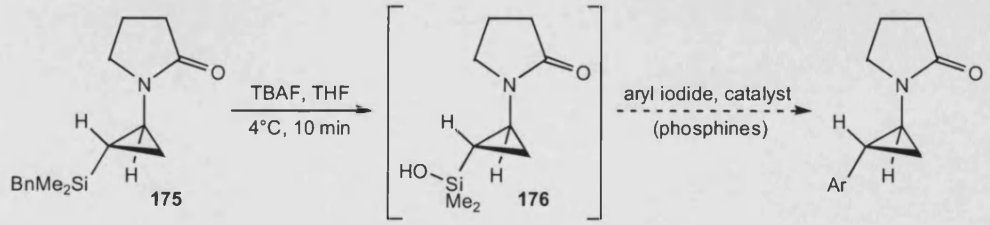
The absolute configuration of **(+)-173A** was determined by its X-Ray diffraction (Scheme 129) and its structure also supports the proposed mechanism for this cyclopropanation reaction (*vide supra*).



Scheme 129

Cyclopropylsilane **175** was also prepared and chosen for the investigation of the cross-coupling reaction, as it was more conveniently prepared from inexpensive *N*-diethoxymethylpyrrolidinone **78**.

The general procedure consisted of the initial *in situ* formation of the corresponding silanol of **176** by treatment with TBAF (2.2 eq) in THF followed by the addition of aryl iodide (1.5 eq), palladium catalyst and, in some cases, phosphines. The reaction mixture was then heated for 20 hours (Scheme 130 and Table 9).



Scheme 130

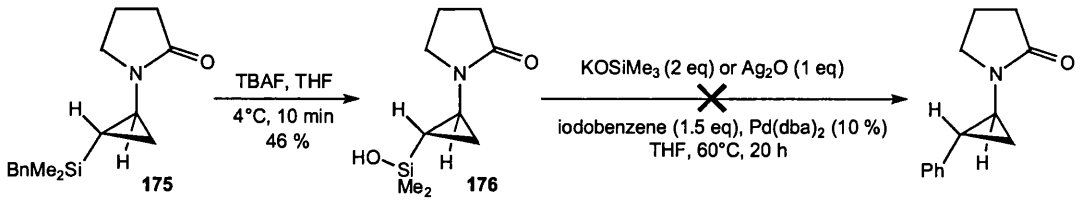
	Aryl iodide	Pd catalyst	Phosphine	Solvent	Temp.
1	iodo benzene	$Pd(dba)_2$ (5%)	—	THF	60°C
2	iodo benzene	$Pd(OAc)_2$ (5%)	PPh_3 (10%)	THF	60°C
3[a]	iodo benzene	$Pd(OAc)_2$ (5%)	PPh_3 (10%)	THF→toluene	110°C
4[a]	iodo-4-nitrobenzene	$Pd(dba)_2$ (10%)	—	THF	100°C

[a] THF was removed after the first step and replaced by toluene. [b] The reaction was performed in a sealed tube.

Table 9

Unfortunately, although silane **175** was completely converted to its corresponding silanol **176**, as evidenced by the ^1H NMR of the crude reaction mixture, none of these reactions actually yielded the desired cross-coupled products. As the oxidative addition of aryl iodides is normally a facile process, the inability of the TBAF-activated silanol **176** to undergo transmetallation could therefore provide a possible explanation for the failure of these reactions.

As silanols are also known to be activated by silver(I) oxide or bases (*vide supra*), we decided to prepare and isolate the silanol **176** and then conduct the cross-coupling reaction with these promoters. Unfortunately, once again, under these conditions no reaction occurred (Scheme 131).



Scheme 131

However, cross-coupling reactions may proceed if the starting cyclopropylsilanes bore more reactive silyl groups, such as trifluorosilane group, but these compounds may not be stable enough under the experimental conditions employed for our methodology.[124] A fine balance between the reactivity and the stability of the silane derivative would

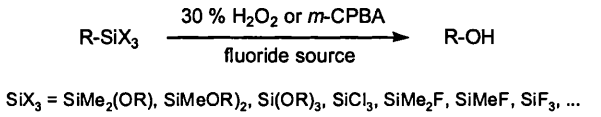
thus have to be found in order to achieve an appropriate cyclopropylsilane coupling partner.

2.10 Preparation of vicinal amino cyclopropanols

Concurrently with the study of palladium-catalysed cross-coupling reactions discussed above, we were also interested in synthesising amino cyclopropanols by the transformation of the silyl moiety of cyclopropylsilanes *via* the Tamao-Fleming oxidation reaction.

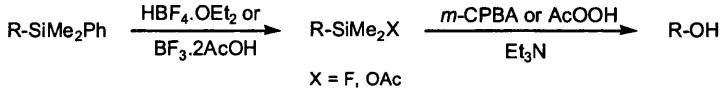
2.10.1 Background

The conversion of a silicon group into a hydroxyl group by the oxidative cleavage of a carbon-silicon bond is a valuable transformation which is widely applied in organic synthesis at the present time.[125] Two different methods have been developed. The first by Tamao and Kumada, relied on the facile oxidative cleavage of a silicon-carbon bond of a silyl group activated by the presence of a heteroatom.[126] This reaction was performed either with hydrogen peroxide or *m*-CPBA in the presence of a source of fluoride, most commonly potassium fluoride (Scheme 132).



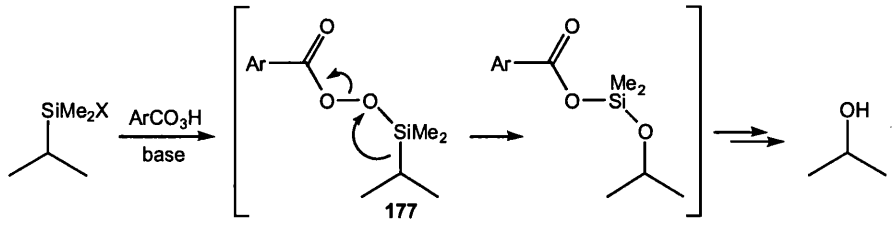
Scheme 132

Independently, Fleming *et al.* described a two step protocol for the conversion of the $SiMe_2Ph$ moiety to a hydroxy group.[127] Their approach consisted of the initial substitution of the phenyl ring through protodesilylation and subsequent oxidation of the carbon-silicon bond of the resulting intermediate (Scheme 133).



Scheme 133

The formation of a silyl peroxide of the type **177** which then underwent a migration analogous to that encountered in a Baeyer-Villiger rearrangement was postulated for this reaction (Scheme 134).[125]

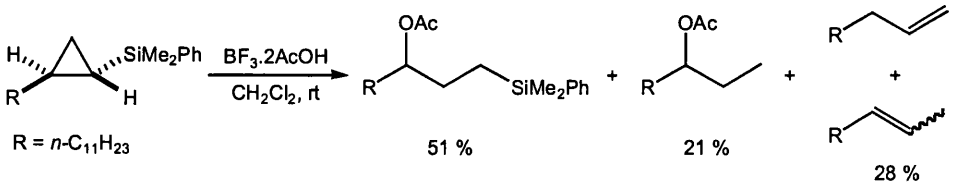


Scheme 134

2.10.2 The use of the Tamao-Fleming oxidation of cyclopropylsilanes leading to the preparation of vicinal amino cyclopropanols

As in the case of the cross-coupling reaction that we attempted to develop using cyclopropylsilanes, the selection of the silyl group for the Tamao-Fleming oxidation was crucial.

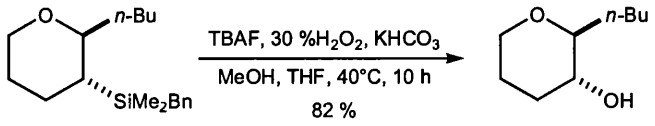
It was expected that reactive silanes, such as trichloro- or fluorosilanes, would not be stable under our cyclopropanation conditions and as a consequence these were not used. Additionally, the electrophilic conditions employed for the protodesilylation of the more robust $SiMe_2Ph$ moiety are known to be incompatible with the presence of a cyclopropane which would undergo ring opening in this situation (Scheme 135).[128]



Scheme 135

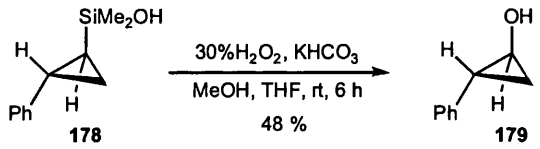
Recently, alternative silyl groups which offer the advantages of having comparable stability to $SiMe_2Ph$ but also being converted to the hydroxyl group under milder conditions have emerged.[129] Amongst these, the benzyldimethylsilyl group, previously

used for our study on cross-coupling reactions, has appeared as a very effective hydroxy surrogate (Scheme 136).[129b]



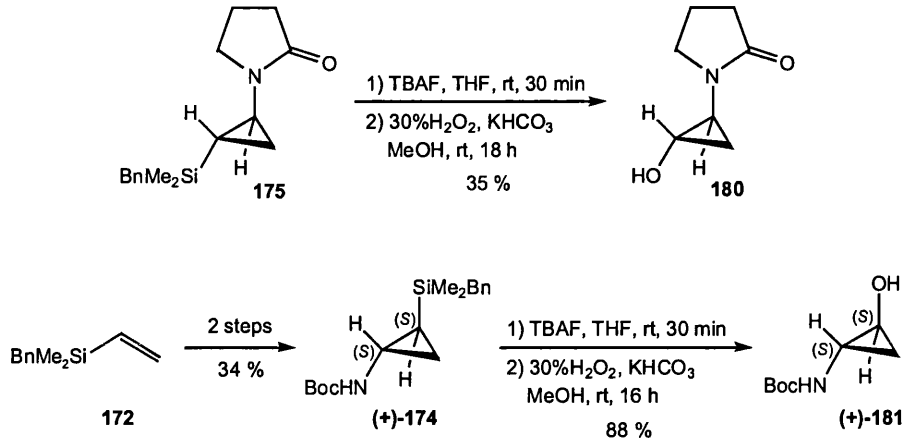
Scheme 136

Also, it has been shown that the cyclopropylsilanol **178** can be converted to its corresponding cyclopropanol **179** using hydrogen peroxide in the presence of an inorganic base thus demonstrating the stability of a cyclopropyl ring under these experimental conditions (Scheme 137).[130]



Scheme 137

In order to synthesise vicinal amino cyclopropanols, we accordingly chose to investigate the oxidation of the carbon-silicon bond of the two cyclopropylsilanes **175** and **(+)-174** prepared previously. The optimum conditions for this sequence were found to involve treatment of the silane with TBAF in the first instance, to form its corresponding silanol *in situ* prior to oxidation (Scheme 138). Both reactions occurred with complete retention of configuration at the carbon centre as reported by Tamao and Fleming.[126b,127b] This 'one pot' procedure was found particularly effective for the synthesis of the chiral *trans* amino alcohol **(+)-181**. Because of its well-defined and rigid structure, this latter compound could be a very interesting and valuable intermediate in medicinal chemistry.



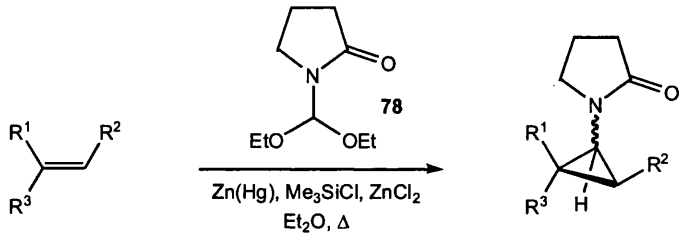
Scheme 138

This study consequently confirmed the versatility of the benzyldimethylsilane group as a robust and very effective latent hydroxyl group and provided the first successful examples of the Tamao-Fleming oxidation of an all-carbon silicon species in the presence of a cyclopropyl ring.

Chapter 3

Conclusions and Perspectives

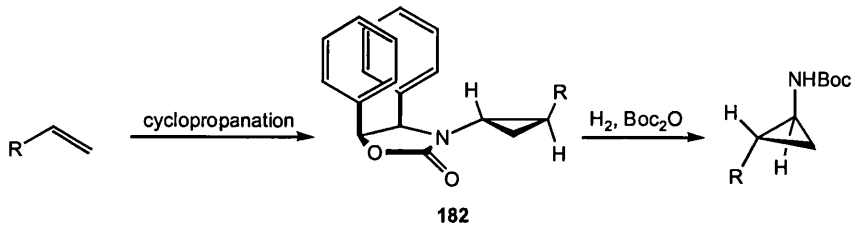
The present work has involved a study of the generation and the reactivity of novel organozinc carbenoids possessing adjacent nitrogen functionalities. Firstly, it was discovered that the presence of an electron-withdrawing group on the nitrogen atom was necessary to ensure the generation and the cyclopropanating ability of the carbenoid species. When derived from an "acetal" moiety, the organozinc carbenoid attached to pyrrolidinone underwent cyclopropanation reactions with a wide range of alkenes. The preferred formation of the less hindered *trans* or *exo* isomer was observed, especially when the alkene employed bore a bulky group (Scheme 139).



Scheme 139

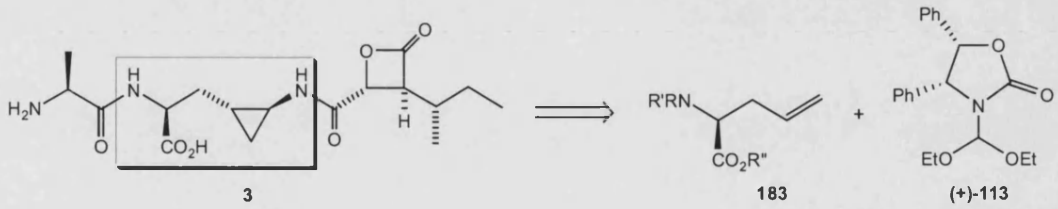
If organozinc carbenoids were generated from an acyclic *N*-diethoxymethyl amide or from an *N*-formyl derivative, the yields of cyclopropanes obtained were lower, showing the advantages of the constrained cyclic amide as the source of the amino functionality and the superior reactivity of the acetal moiety.

The value of this methodology was greatly increased when primary aminocyclopropanes were found to be accessible from diphenyloxazolidinone derivatives of type **182** (Scheme 140). Chiral protected aminocyclopropanes were thus prepared in only two steps from alkenes (Scheme 140).



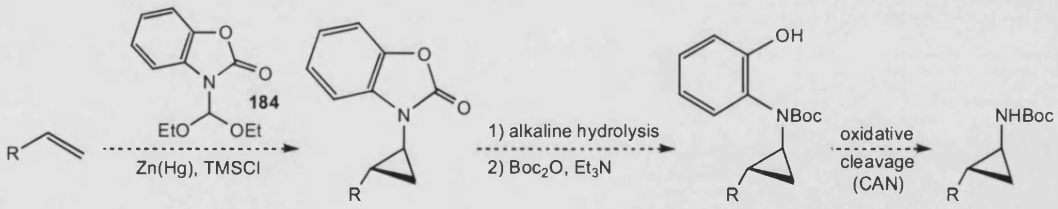
Scheme 140

In terms of future work in this area, it would certainly be of interest to assess the efficiency of this newly developed methodology by applying it towards the synthesis of both natural and non-natural molecules of biological importance. Thus, a concise synthesis of 3-(*trans*-2-aminocyclopropyl)alanine, a component of the antitumor agent Belactosin A **3** could be envisaged from the allylglycine derivative **183** (Scheme 141).



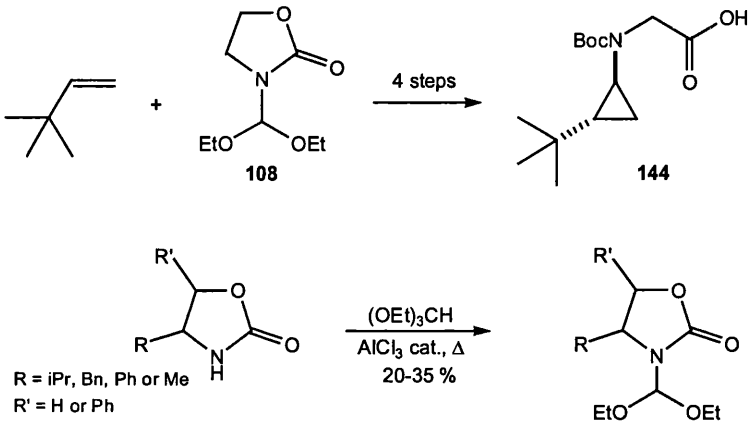
Scheme 141

However aryl substituted cyclopropylamines were found not to be accessible using the methodology involving the use of *N*-diethoxymethyl diphenyloxazolidinone **113** since the cyclopropyl ring underwent hydrogenolysis during the hydrogenation step. In a complementary strategy to those different alternative approaches already investigated, the use of **184** as a carbenoid precursor could also be considered, since the amine functionality could be revealed after hydrolysis of the oxazolidinone ring and oxidation, two steps both of which should be compatible with the presence of the cyclopropane ring (Scheme 142).



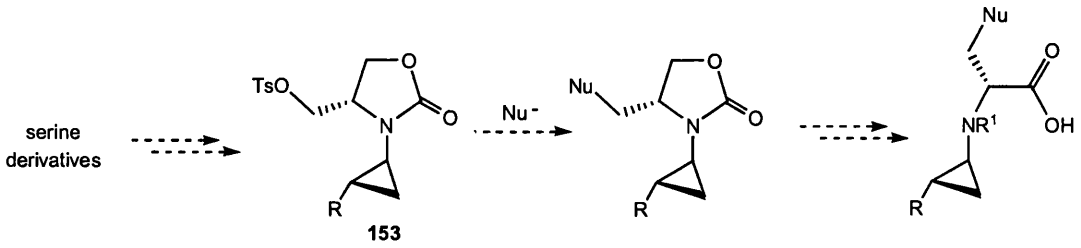
Scheme 142

The preparation of *N*-substituted amino acids by cyclopropanation of alkenes with diverse *N*-diethoxymethyl oxazolidinones was also studied. Even although the reference compound **144** was obtained following this approach, the curious variation in yield as a function of substitution pattern around the oxazolidinone ring when synthesising a range of *N*-diethoxymethyl oxazolidinones prompted us to abandon this route (Scheme 143).



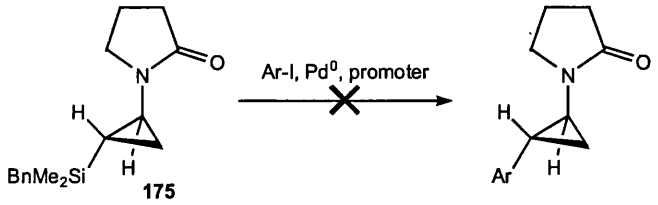
Scheme 143

Alternatively, the tosylate **153** derived from serine derivatives could be employed as a modifiable scaffold and thus lead to the formation of a wide range of natural and unnatural *N*-substituted amino acids (Scheme 144). However, in order to become a more general method, this would require finding a serine derivative which would exhibit a high degree of stereocontrol in the cyclopropanation reaction.



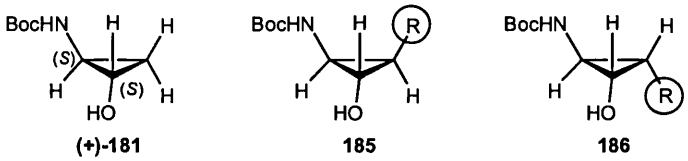
Scheme 144

Cyclopropylsilanes were tested as substrates in palladium-catalysed cross-coupling reactions with aryl iodides. However these reactions did not yield any of the desired products, probably due the failure of the silyl component to undergo transmetallation (Scheme 145). Employing more reactive silicon groups and different catalysts and/or additives might encourage the reaction to proceed.



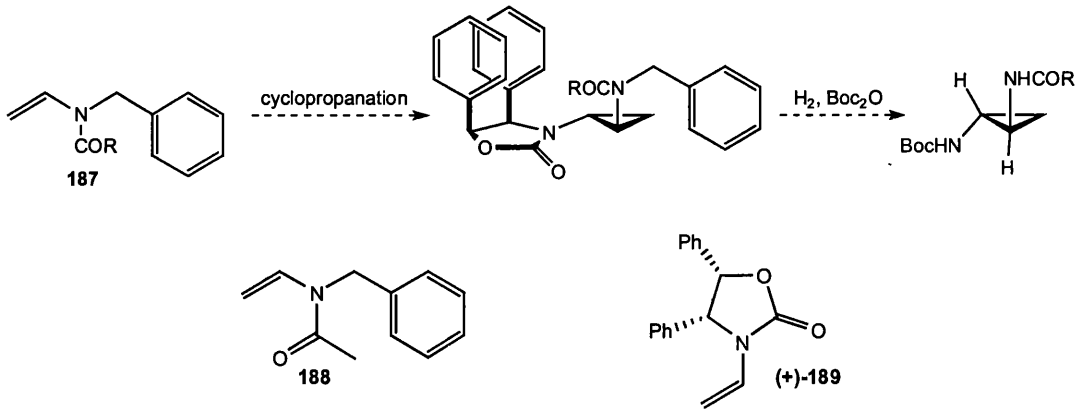
Scheme 145

By way of contrast however, the Tamao-Fleming oxidation was successfully applied to cyclopropylsilanes prepared using our methodology. This work allowed us to synthesise the structurally rigid chiral amino cyclopropanol **(+)-181** (Scheme 146). As (*Z*) and (*E*) alkenylsilanes are easily accessible, it will be of interest to extend this methodology to substituted cyclopropanols of type **185** and **186** (Scheme 146).[115,123]



Scheme 146

Equally interesting would be the preparation of chiral *trans* diamines. These compounds could be conveniently synthesised from the cyclopropanation of enamide of type **187** (Scheme 147). However, preliminary studies on the cyclopropanation of the enamides **188** and **(+)-189** have indicated that our standard experimental conditions must be modified to increase the stability of the zinc amalgam in the presence of such functionalised alkenes.



Scheme 147

Although this newly developed methodology allows for the rapid and easy preparation of aminocyclopropanes derivatives, the cyclopropanation reactions currently proceed only in moderate to good yields, undoubtedly due to the ability of zinc amalgam to form aggregates. The inability to predict for any given substrate and carbenoid precursor whether or not such destructive physical characteristics will occur has been an ongoing frustration. It would thus be very interesting to investigate the reactivity of other metallocarbenoids which could be generated from different electron donor metals such as indium or ytterbium.

Chapter 4

Experimental

4.1 General information

Melting points were determined using a Reichert hot-stage apparatus and are uncorrected. Optical rotations were measured using a Perkin-Elmer 241 (using the sodium D-line, 529 nm) polarimeter and $[\alpha]_D^T$ values are given in 10^{-1} deg cm^2 g^{-1}, concentration (*c*) in g per 100 mL. Infrared (IR) were recorded on a Perkin-Elmer 1605 Fourier transform spectrometer, and were recorded as thin films (NaCl) either of pure sample or of solution of sample in the stated solvent. Absorption maxima are reported in wavenumbers (cm^{-1}). Only selected absorbances are reported.

^1H NMR spectra were recorded at 300 MHz on a Bruker AMX300 spectrometer, at 400 MHz on a Bruker AMX400 spectrometer or at 500 MHz on a Bruker Avance 500 spectrometer in the stated solvent using residual protic solvent $CHCl_3$ (δ = 7.24 ppm, s), DMSO (δ = 2.49 ppm, qn) or CH_6Cl_6 (δ = 7.15 ppm, s) as the internal standard. Chemical shifts are quoted in ppm using the following abbreviations: s, singlet; d, doublet; t, triplet; q, quartet; qn, quintet; m, multiplet; br, broad or a combination of these. The coupling constants (*J*) are reported as measured and recorded in Hertz.
2D-noesy NMR experiments were carried out on a Bruker Avance 500 spectrometer.
^{13}C NMR spectra were recorded at 75 MHz on a Bruker AMX300 spectrometer, at 100 MHz on a Bruker AMX400 spectrometer or at 125 MHz on a Bruker Avance 500 spectrometer in the stated solvent using the central reference of $CHCl_3$ (δ = 77.0 ppm, t), DMSO (δ = 39.5 ppm, septuplet) or CH_6Cl_6 (δ = 128.0 ppm, s) as the internal standard. Chemical shifts are reported to the nearest 0.1 ppm. If more than one peak is observed within 0.1 ppm accuracy, the number of peaks will be indicated.

Mass spectra and accurate mass measurements were recorded on a Micromass 70-SE Magnetic Sector spectrometer at the University College London Chemistry department. Elementary analyses were performed at University College London Chemistry department. The X-ray crystal structure of **(+)-173** was determined using a Bruker Smart Apex diffractometer at the University College London Chemistry department.

All reactions using dry solvents were carried out in oven-dried glassware under a nitrogen atmosphere. Diethyl ether and THF were distilled from sodium-benzophenone ketyl. Toluene was distilled from sodium. DMF was distilled under reduced pressure from calcium hydride and stored over 4Å molecular sieves. Methanol was distilled from magnesium turnings and iodine. Triethylamine was pre-dried with potassium hydroxide pellets, filtered, distilled and stored over potassium hydroxide pellets. Chlorotrimethylsilane was distilled from calcium hydride immediately prior to use.

Analytical thin layer chromatography was performed on aluminium sheets pre-coated with Merck silica gel 60 F_{254}, and visualised with ultraviolet light (254nm), plus either basic potassium permanganate or acidic ammonium molybdate solution. Flash chromatography was performed using BDH silica gel (40-60μm).

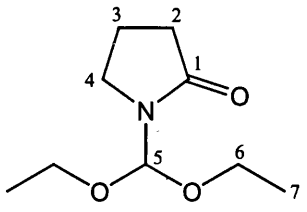
All compounds were used as supplied by the manufacturers unless otherwise stated.

Zinc amalgam

Zinc dust (10.0 g, 153 mol) was added to a vigorously stirred solution of mercury (II) chloride (2.0 g, 7.20 mmol) and concentrated aqueous solution of hydrochloric acid (12M, 0.5 mL) in water (30 mL). The mixture was stirred for 10 minutes, the zinc filtered off and then washed with water (3 x 20 mL), acetone (3 x 20 mL), ethanol (3 x 20 mL) and ether (3 x 20 mL) before being dried under high vacuum. The zinc amalgam was thereafter stored under vacuum, and was always flame dried under a stream of nitrogen immediately prior to use.

4.2 Experimental Procedures

N-Diethoxymethyl-2-pyrroldinone 78

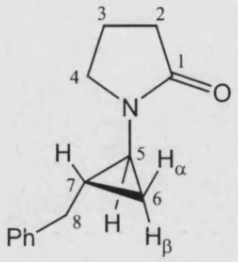
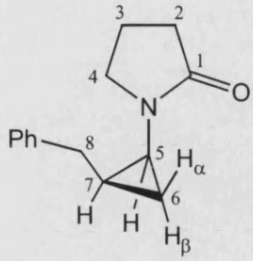


$C_9H_{17}NO_3$ 187.24 g.mol^{-1}

The *title compound* was prepared by a literature method.[93] A mixture of 2-pyrrolidinone (2.0 g, 23.5 mmol, 1 eq), aluminium chloride (0.31 g, 2.35 mmol, 0.1 eq) and triethyl orthoformate (77.3 mL, 0.47 mol, 20 eq) was heated at 150°C for 48 h. The reaction mixture was cooled to room temperature and then quenched with saturated aqueous $NaHCO_3$ solution (35 mL). The aqueous phase was extracted with diethyl ether (70 mL then 35 mL) and the combined organic extracts were washed with brine (35 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (silica, P.E. 30-40°C/EtOAc 3:2 to 1:1) to give the *title compound* **78** (3.08 g, 16.45 mmol, 70%) as a yellow oil.

R_f (P.E. 30-40°C/EtOAc 1:1) 0.33; **IR** (film): ν_{max} 2977 (s), 2897 (m), 1693 (s, C=O), 1418 (s), 1104 (s), 1062 (s) cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$): δ 1.20 (t, $^3J_{7\text{-}6}$=7.0 Hz, 6H, H_7), 2.00 (qn, $^3J_{3\text{-}2}$=$^3J_{3\text{-}4}$=7.9 Hz, 2H, H_3), 2.41 (t, $^3J_{2\text{-}3}$=8.2 Hz, 2H, H_2), 3.42 (t, $^3J_{4\text{-}3}$=7.3 Hz, 2H, H_4), 3.48 (dq, $^3J_{6\text{-}7}$=7.0 Hz, ^2J=9.4 Hz, 2H, H_6), 3.62 (dq, $^3J_{6\text{-}7}$=7.0 Hz, ^2J=9.4 Hz, 2H, H_6), 5.87 (s, 1H, H_5); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 14.5 (C_7), 17.8 (C_3), 31.4 (C_2), 40.5 (C_4), 61.9 (C_6), 98.8 (C_5), 175.2 (C_1); **EI-MS** *m/z* (%): 188 (MH^+, 4), 142 ([M-OC_2H_5]$^+$, 100); **HMRS**: MH^+, found 188.13052. $C_9H_{18}NO_3$ requires 188.12867.

1-(2-Benzylcyclopropyl)-2-pyrrolidinone 79

trans   *cis*

$C_{14}H_{17}NO$ 215.29 g.mol^{-1}

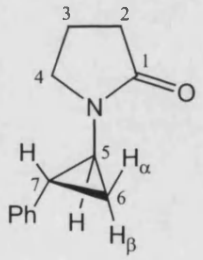
A solution of *N*-diethoxymethy-2-pyrrolidinone **78** (0.393 g, 2.11 mmol, 2 eq) in dry diethyl ether (3 mL) was added *via* a motorised syringe pump over 14 h to a vigorously stirred mixture of zinc amalgam (1.38 g, 21.1 mmol, 20 eq), anhydrous zinc chloride (0.29 g, 2.11 mmol, 2 eq), chlorotrimethylsilane (1.34 mL, 10.56 mmol, 10 eq) and freshly distilled allylbenzene (0.125 g, 1.06 mmol, 1 eq) in dry diethyl ether (5.5 mL) under nitrogen at reflux. The mixture was stirred for 6 h and then allowed to cool to room temperature. The reaction was quenched with saturated aqueous $NaHCO_3$ solution (20 mL) and after stirring for 20 min, the mixture was filtered through celite and the separated zinc washed with diethyl ether (20 mL) and dichloromethane (20 mL). The organic solvents were removed *in vacuo* and the aqueous layer was extracted with diethyl ether (3 x 20 mL). The combined organic extracts were washed with brine (20 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (silica, EtOAc/MeOH 99:1 to 98:2) to give an inseparable mixture of *cis* and *trans* cyclopropanes **79** (0.199 g, 0.93 mmol, 88%, *trans*/*cis*: 11.5:1 as determined by ^{1}H NMR) as a colourless oil.

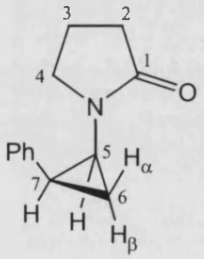
R_f (EtOAc/MeOH 98:2) 0.35; **IR** (mixture of *trans* and *cis*, film): ν_{max} 2992 (m), 2958 (m), 1688 (s, C=O), 1495 (m), 1454 (m), 1421 (s), 1292 (s), 1030 (w), 742 (m), 700 (m) cm^{-1}; **^{1}H NMR** (*trans*, 500 MHz, $CDCl_3$): δ 0.75 (ddd, $^2J_{6\beta\text{-}6\alpha}$=5.8 Hz, $^3J_{6\beta\text{-}7}$=6.1 Hz, $^3J_{6\beta\text{-}5}$=7.5 Hz, 1H, $H_{6\beta}$), 0.95 (ddd, $^3J_{6\alpha\text{-}5}$=4.1 Hz, $^2J_{6\alpha\text{-}6\beta}$=5.8 Hz, $^3J_{6\alpha\text{-}7}$=9.4 Hz, 1H, $H_{6\alpha}$), 1.28 (dddt, $^3J_{7\text{-}5}$=3.5 Hz, $^3J_{7\text{-}6\beta}$=6.1 Hz, $^3J_{7\text{-}8}$=6.9 Hz, $^3J_{7\text{-}6\alpha}$=9.4 Hz, 1H, H_7), 1.86-1.93 (m, 2H, H_3), 2.32 (t, $^3J_{2\text{-}3}$=8.0 Hz, 2H, H_2), 2.50-2.55 (m, 2H, H_5 and H_8), 2.70 (dd, $^3J_{8\text{-}7}$=6.7 Hz, ^2J=14.7 Hz, 1H, H_8), 3.16 (t, $^3J_{4\text{-}3}$=7.0 Hz, 2H, H_4), 7.18-7.30 (m, 5H, H_{arom}); **^{13}C NMR** (*trans*, 125 MHz, $CDCl_3$): δ 12.1 (C_6), 17.8 (C_3), 19.0 (C_7), 31.6

(C_2 and C_5), 38.0 (C_8), 47.2 (C_4), 125.9 (CH), 128.2 (CH), 140.5 (C_q), 175.8 (C_1); **^{1}H NMR** (*cis*, 500 MHz, $CDCl_3$): δ 0.71 (ddd, $^3J_{6\alpha\text{-}5}$=4.6 Hz, $^2J_{6\alpha\text{-}6\beta}$=6.0 Hz, $^3J_{6\alpha\text{-}7}$=6.3 Hz, 1H, $H_{6\alpha}$), 1.00 (ddd, $^2J_{6\beta\text{-}6\alpha}$=6.0 Hz, $^3J_{6\beta\text{-}5}$=8.0 Hz, $^3J_{6\beta\text{-}7}$=8.8 Hz, 1H, $H_{6\beta}$), 1.34 (dddt, $^3J_{7\text{-}8}$=4.9 Hz, $^3J_{7\text{-}6\alpha}$=6.5 Hz, $^3J_{7\text{-}5}$=7.1 Hz, $^3J_{7\text{-}6\beta}$=$^3J_{7\text{-}8}$=8.9 Hz, 1H, H_7), 1.94-2.01 (m, 2H, H_3), 2.19 (dd, $^3J_{8\text{-}7}$=9.0 Hz, ^2J=14.4 Hz, 1H, H_8), 2.38-2.42 (m, 2H, H_2), 2.66 (ddd, $^3J_{5\text{-}6\alpha}$=4.6 Hz, $^3J_{5\text{-}7}$=7.0 Hz, $^3J_{5\text{-}6\beta}$=8.0 Hz, 1H, H_5), 3.02 (dd, $^3J_{8\text{-}7}$=4.8 Hz, ^2J=14.4 Hz, 1H, H_8), 3.29-3.39 (m, 2H, H_4), 7.18-7.30 (m, 5H, H_{arom}); **^{13}C NMR** (*cis*, 125 MHz, $CDCl_3$): δ 10.3 (C_6), 18.2 (C_3), 18.5 (C_7), 30.4 (C_5), 31.6 (C_2), 33.8 (C_8), 49.1 (C_4), 125.8 (CH), 128.2 (CH), 141.1 (C_q), 176.9 (C_1); **FAB-MS** *m/z* (%): 216 (MH^+, 100), 124 ($[M\text{-}Bn]^+$, 63), 91 (Bn^+,29); **HMRS**: M^+, found 215.13149. $C_{14}H_{17}NO$ requires 215.1310.

1-(2-Phenylcyclopropyl)-2-pyrrolidinone 82

trans





cis

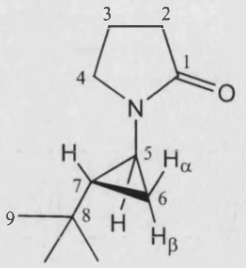
$C_{13}H_{15}NO$ 201.27 g.mol^{-1}

A solution of *N*-diethoxymethy-2-pyrrolidinone **78** (0.50 g, 2.70 mmol, 2 eq) in dry diethyl ether (2 mL) was added *via* a motorised syringe pump over 2 h to a vigorously stirred mixture of zinc amalgam (1.77 g, 27.0 mmol, 20 eq), anhydrous zinc chloride (0.37 g, 2.70 mmol, 2 eq), chlorotrimethylsilane (1.71 mL, 13.5 mmol, 10 eq) and freshly distilled styrene (0.141 g, 1.35 mmol, 1 eq) in dry diethyl ether (9 mL) under nitrogen at reflux. The reaction mixture was cooled to room temperature and then stirred for 12 h. The reaction was quenched with saturated aqueous $NaHCO_3$ solution (20 mL) and after stirring for 20 min, the mixture was filtered through celite and the separated zinc washed with diethyl ether (20 mL) and dichloromethane (20 mL). The organic solvents were removed *in vacuo* and the aqueous layer was extracted with diethyl ether (3 x 20 mL). The combined organic extracts were washed with brine (20 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude product was purified by flash

column chromatography (silica, EtOAc) to give a mixture mixture of *cis* and *trans* cyclopropanes **82** (0.189 g, 0.94 mmol, 70%, *trans*/*cis*: 1.1:1 as determined by ^{1}H NMR) as a colourless oil.

R_f (EtOAc) 0.42; **IR** (mixture of *trans* and *cis*, film): ν_{max} 2980 (s), 2886 (s), 1680 (s, C=O), 1499 (m), 1459 (m), 1030 (w), 773 (w), 737 (w), 701 (s) cm^{-1}; **^{1}H NMR** (*trans*, 500 MHz, $CDCl_3$): δ 1.28 (td, $^2J_{6\beta\text{-}6\alpha}$=$^3J_{6\beta\text{-}7}$=6.3 Hz, $^3J_{6\beta\text{-}5}$=7.6 Hz, 1H, $H_{6\beta}$), 1.39 (ddd, $^3J_{6\alpha\text{-}5}$=4.6 Hz, $^2J_{6\alpha\text{-}6\beta}$=6.0 Hz, $^3J_{6\alpha\text{-}7}$=9.7 Hz, 1H, $H_{6\alpha}$), 1.96-2.03 (m, 2H, H_3), 2.17 (ddd, $^3J_{7\text{-}5}$=3.5 Hz, $^3J_{7\text{-}6\beta}$=6.5 Hz, $^3J_{7\text{-}6\alpha}$=9.9 Hz, 1H, H_7), 2.39 (t, $^3J_{2\text{-}3}$=8.1 Hz, 2H, H_2), 2.78 (ddd, $^3J_{5\text{-}7}$=3.7 Hz, $^3J_{5\text{-}6\alpha}$=4.5 Hz, $^3J_{5\text{-}6\beta}$=7.8 Hz, 1H, H_5), 3.35-3.40 (m, 2H, H_4), 7.10-7.19 (m, 3H, H_{arom}), 7.22-7.28 (m, 2H, H_{arom}); **^{13}C NMR** (*trans*, 125 MHz, $CDCl_3$): δ 14.7 (C_6), 18.1 (C_3), 22.7 (C_7), 31.8 (C_2), 34.9 (C_5), 47.5 (C_4), 126.1 (CH), 126.4 (CH), 128.4 (CH), 140.4 (C_q), 175.9 (C_1); **^{1}H NMR** (*cis*, 500 MHz, $CDCl_3$): δ 1.37 (ddd, $^2J_{6\beta\text{-}6\alpha}$=6.8 Hz, $^3J_{6\beta\text{-}5}$=8.0 Hz, $^3J_{6\beta\text{-}7}$=9.1 Hz, 1H, $H_{6\beta}$), 1.45-1.53 (m, 1H, H_3), 1.56-1.65 (m, 2H, H_3 and $H_{6\alpha}$), 2.10-2.22 (m, 3H, H_2 and H_7), 2.64 (ddd, $^3J_{4\text{-}3}$=4.8 Hz, $^3J_{4\text{-}3}$=8.5 Hz, ^2J=9.5 Hz, 1H, H_4), 2.79 (dt, $^3J_{5\text{-}6\alpha}$=4.9 Hz, $^3J_{5\text{-}7}$=$^3J_{5\text{-}6\beta}$=7.6 Hz, 1H, H_5), 2.85 (ddd, ^3J=6.8 Hz, ^3J=8.0 Hz, ^2J=9.5 Hz, 1H, H_4), 7.07-7.14 (m, 3H, H_{arom}), 7.17-7.21 (m, 2H, H_{arom}); **^{13}C NMR** (*cis*, 125 MHz, $CDCl_3$): δ 10.7 (C_6), 18.0 (C_3), 21.7 (C_7), 31.5 (C_2), 32.4 (C_5), 48.0 (C_4), 126.1 (CH), 127.8 (CH), 127.9 (CH), 136.8 (C_q), 176.7 (C_1); **EI-MS** *m/z* (%): 201 (M^+, 7), 172 (21), 144 (24), 130 (69), 115 (100), 103 (72), 91 (Bn^+, 52), 77 (Ph^+, 74); **HMRS**: M^+, found 201.11549. $C_{13}H_{15}NO$ requires 201.11482.

1-(2-*tert*-Butylcyclopropyl)-2-pyrrolidinone 83



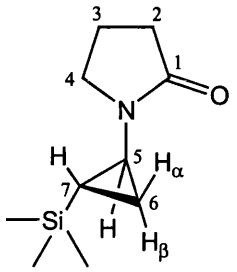
$C_{11}H_{19}NO$ 181.28 g.mol^{-1}

A solution of *N*-diethoxymethy-2-pyrrolidinone **78** (0.66 g, 3.56 mmol, 2 eq) in dry diethyl ether (3.5 mL) was added *via* a motorised syringe pump over 14 h to a vigorously stirred mixture of zinc amalgam (2.33 g, 35.64 mmol, 20 eq), zinc chloride (1M solution in diethyl ether, 3.56 mL, 3.56 mmol, 2 eq), chlorotrimethylsilane (2.26 mL, 17.8 mmol, 10 eq) and 3,3-dimethylbut-1-ene (0.15 g, 1.78 mmol, 1 eq) in dry diethyl ether (4 mL) under nitrogen at reflux. The mixture was stirred for 6 h and then allowed to cool to room temperature. The reaction was quenched with saturated aqueous $NaHCO_3$ solution (20 mL) and after stirring for 20 min, the mixture was filtered through celite and the separated zinc washed with diethyl ether (20 mL) and dichloromethane (20 mL). The organic solvents were removed *in vacuo* and the aqueous layer was extracted with diethyl ether (3 x 20 mL). The combined organic extracts were washed with brine (20 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude product (*trans*/*cis*: >95:<5 as determined by ^{1}H NMR) was purified by flash column chromatography (silica, EtOAc/P.E. 30-40°C 88:12) to give almost exclusively the *trans* cyclopropane **83** (0.197 g, 1.08 mmol, 61%) as a colourless oil.

R_f (EtOAc/P.E. 40-60°C 9:1) 0.30; **IR** (film): ν_{max} 2955 (s), 2868 (m), 1694 (s, C=O), 1462 (m), 1421 (s), 1296 (s), 1192 (w), 1022 (w), 905 (w), 845 (w) cm^{-1}; **^{1}H NMR** (*trans*, 500 MHz, $CDCl_3$): δ 0.67-0.74 (m, 2H, $H_{6\alpha}$ and $H_{6\beta}$), 0.81 (s, 9H, H_9), 0.86 (ddd, $^3J_{7\text{-}5}$=4.1 Hz, $^3J_{7\text{-}6\beta}$=6.8 Hz, $^3J_{7\text{-}6\alpha}$=9.9 Hz, 1H, H_7), 1.84-1.94 (m, 2H, H_3), 2.29 (t, $^3J_{2\text{-}3}$=8.2 Hz, 2H, H_2), 2.47 (td, $^3J_{5\text{-}6\alpha}$=$^3J_{5\text{-}7}$=4.1 Hz, $^3J_{5\text{-}6\beta}$=7.5 Hz, 1H, H_5), 3.26 (t, $^3J_{4\text{-}3}$=7.1 Hz, 2H, H_4); **^{13}C NMR** (*trans*, 125 MHz, $CDCl_3$): δ 8.7 (C_6), 17.9 (C_3), 28.1 (C_5 and C_9), 29.0 (C_8), 29.5 (C_7), 31.8 (C_2), 47.5 (C_4), 175.8 (C_1); **EI-MS** *m/z* (%):

181 (M^+, 20), 166 ($[M-CH_3]^+$, 10), 124 ($[M-C_4H_9]^+$, 100), 96 (29), 81 (23), 69 (14), 57 ($C_4H_9^+$, 12); **HMRS**: M^+, found 181.146380. $C_{11}H_{19}NO$ requires 181.146655.

1-(2-Trimethylsilanylcyclopropyl)-2-pyrrolidinone 84



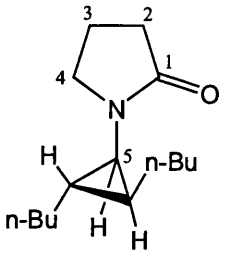
$C_{10}H_{19}NOSi$ 197.35 g.mol^{-1}

A solution of *N*-diethoxymethy-2-pyrrolidinone **78** (0.56 g, 3.0 mmol, 2 eq) in dry diethyl ether (4 mL) was added *via* a motorised syringe pump over 16 h to a vigorously stirred mixture of zinc amalgam (1.95 g, 30 mmol, 20 eq), zinc chloride (1M solution in diethyl ether, 3 mL, 3 mmol, 2 eq), chlorotrimethylsilane (1.9 mL, 15 mmol, 10 eq) and vinyltrimethylsilane (0.15 g, 1.5 mmol, 1 eq) in dry diethyl ether (5 mL) under nitrogen at reflux. The mixture was stirred for 6 h and then allowed to cool to room temperature. The reaction was quenched with saturated aqueous $NaHCO_3$ solution (20 mL) and after stirring for 20 min, the mixture was filtered through celite and the separated zinc washed with diethyl ether (20 mL) and dichloromethane (20 mL). The organic solvents were removed *in vacuo* and the aqueous layer was extracted with diethyl ether (3 x 20 mL). The combined organic extracts were washed with brine (20 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude product (*trans/cis*: >95:<5 as determined by ^{1}H NMR) was purified by flash column chromatography (silica, EtOAc/P.E. 30-40°C 7:3) to give almost exclusively the *trans* cyclopropane **84** (0.172 g, 0.87 mmol, 58%) as a colourless oil.

R_f (EtOAc/P.E. 40-60°C 7:3) 0.35; **IR** (film): ν_{max} 2954 (s), 2894 (m), 1694 (s, C=O), 1419 (s), 1375 (m), 1296 (m), 1249 (s, Si-C), 886 (s), 837 (s, Si-C), 753 (m) cm^{-1}; **^{1}H NMR** (*trans*, 500 MHz, $CDCl_3$): δ -0.12 (ddd, $^3J_{7\text{-}5}$=5.3 Hz, $^3J_{7\text{-}6\beta}$=8.2 Hz, $^3J_{7\text{-}6\alpha}$=11.3 Hz, 1H, H_7), -0.06 (s, 9H, $Si(CH_3)_3$), 0.63 (ddd, $^2J_{6\beta\text{-}6\alpha}$=4.8 Hz, $^3J_{6\beta\text{-}5}$=6.7 Hz, $^3J_{6\beta\text{-}7}$=8.2 Hz, 1H, $H_{6\beta}$), 0.89 (ddd, $^3J_{6\alpha\text{-}5}$=3.6 Hz, $^2J_{6\alpha\text{-}6\beta}$=4.8 Hz, $^3J_{6\alpha\text{-}7}$=11.3 Hz, 1H, $H_{6\alpha}$),

1.84-1.94 (m, 2H, H_3), 2.31 (t, $^3J_{2\text{-}3}$=8.0 Hz, 2H, H_2), 2.50 (ddd, $^3J_{5\text{-}6\alpha}$=3.6 Hz, $^3J_{5\text{-}7}$=5.3 Hz, $^3J_{5\text{-}6\beta}$=6.2 Hz, 1H, H_5), 3.18-3.22 (m, 2H, H_4); **^{13}C NMR** (*trans*, 125 MHz, $CDCl_3$): δ -2.6 (CH_3), 4.2 (C_7), 8.6 (C_6), 18.0 (C_3), 29.1 (C_5), 31.2 (C_2), 47.2 (C_4), 175.8 (C_1); **EI-MS** *m/z* (%): 197 (M^+, 40), 182 ($[M\text{-}CH_3]^+$, 66), 168 ($[M\text{-}C_2H_5]^+$, 36), 154 (27), 142 (66), 124 ($[M\text{-}SiC_3H_9]^+$, 11), 73 ($SiC_3H_9^+$, 100), 59 (22); **HMRS**: M^+, found 197.12332. $C_{10}H_{19}NOSi$ requires 197.12355.

1-(2,3-Dibutylcyclopropyl)-2-pyrrolidinone 85



$C_{15}H_{27}NO$ 237.28 g.mol^{-1}

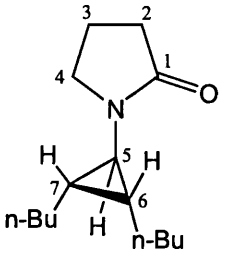
A solution of *N*-diethoxymethy-2-pyrrolidinone **78** (0.53 g, 2.85 mmol, 2 eq) in dry diethyl ether (4 mL) was added *via* a motorised syringe pump over 16 h to a vigorously stirred mixture of zinc amalgam (1.86 g, 28.5 mmol, 20 eq), anhydrous zinc chloride (0.39 g, 2.85 mmol, 2 eq), chlorotrimethylsilane (1.80 mL, 14.25 mmol, 10 eq) and *trans*-dec-5-ene (0.2 g, 1.42 mmol, 1 eq) in dry diethyl ether (7 mL) under nitrogen at reflux. The mixture was stirred for 6 h and then allowed to cool to room temperature. The reaction was quenched with saturated aqueous $NaHCO_3$ solution (20 mL) and after stirring for 20 min, the mixture was filtered through celite and the separated zinc washed with diethyl ether (20 mL) and dichloromethane (20 mL). The organic solvents were removed *in vacuo* and the aqueous layer was extracted with diethyl ether (3 x 20 mL). The combined organic extracts were washed with brine (20 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (silica, EtOAc/P.E. 30-40°C 3:2) to give the cyclopropane **85** (0.28 g, 1.25 mmol, 88%) as a colourless oil.

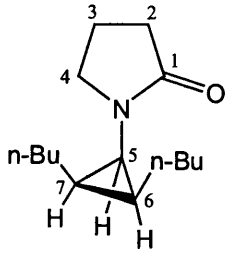
R_f (EtOAc/P.E. 40-60°C 3:2) 0.43; **IR** (film): ν_{max} 2954 (s), 2924 (s), 2856 (m), 1694 (s, C=O), 1416 (m), 1293 (s) cm^{-1}; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 0.68-0.79 (m, 3H), 0.82 (t, ^3J=7.0 Hz, 3H, CH_3), 0.83 (t, ^3J=7.0 Hz, 3H, CH_3), 1.14-1.36 (m, 10H),

1.45-1.53 (m, 1H), 1.87-1.96 (m, 2H, H_3), 2.25 (dd, ^3J=4.2 Hz, ^3J=6.4 Hz, 1H, H_5), 2.32 (t, $^3J_{2\text{-}3}$=8.0 Hz, 2H, H_2), 3.20-3.31 (m, 2H, H_4); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 13.9 (CH_3), 14.0 (CH_3), 18.8 (C_3), 22.4 (CH_2), 22.5 (CH_2), 24.1 (CH), 25.5 (CH), 27.5 (CH_2), 31.0 (CH_2), 31.6 (CH_2 and C_2), 32.5 (CH_2), 36.6 (C_5), 49.0 (C_4), 176.6 (C_1); **EI-MS** *m/z* (%): 237 (M^+, 43), 194 ($[M\text{-}C_3H_7]^+$, 21), 180 ($[M\text{-}C_4H_9]^+$, 100), 138 ($[M\text{-}C_7H_{15}]^+$, 15), 124 ($[M\text{-}C_8H_{17}]^+$, 35), 98 (53), 86 (35), 67 ($C_5H_7^+$, 13), 55 (15); **HMRS**: M^+, found 237.2084. $C_{15}H_{27}NO$ requires 237.20925.

1-(2,3-Dibutylcyclopropyl)-2-pyrrolidinone 86

trans





cis

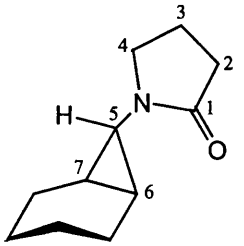
$C_{15}H_{27}NO$ 237.28 g.mol^{-1}

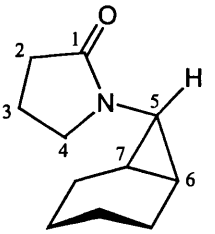
A solution of *N*-diethoxymethy-2-pyrrolidinone **78** (0.48 g, 2.57 mmol, 2 eq) in dry diethyl ether (3.5 mL) was added *via* a motorised syringe pump over 14 h to a vigorously stirred mixture of zinc amalgam (1.68 g, 25.7 mmol, 20 eq), anhydrous zinc chloride (0.31 g, 2.57 mmol, 2 eq), chlorotrimethylsilane (1.63 mL, 12.85 mmol, 10 eq) and *cis*-dec-5-ene (0.18 g, 1.28 mmol, 1 eq) in dry diethyl ether (6.7 mL) under nitrogen at reflux. The mixture was stirred for 6 h and then allowed to cool to room temperature. The reaction was quenched with saturated aqueous $NaHCO_3$ solution (20 mL) and after stirring for 20 min, the mixture was filtered through celite and the separated zinc washed with diethyl ether (20 mL) and dichloromethane (20 mL). The organic solvents were removed *in vacuo* and the aqueous layer was extracted with diethyl ether (3 x 20 mL). The combined organic extracts were washed with brine (20 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (silica, EtOAc/P.E. 30-40°C 3:2) to give an inseparable mixture of *cis* and *trans* cyclopropanes **86** (0.142 g, 0.60 mmol, 47%, *trans/cis* 1:1 as determined by ^{1}H NMR) as a colourless oil.

R_f (EtOAc/P.E. 40-60°C 3:2) 0.4; **IR** (mixture of *trans* and *cis*, film): ν_{max} 2956 (s), 2929 (s), 2857 (m), 1699 (s, C=O), 1464 (m), 1417 (m), 1293 (m), 1251 (w) cm^{-1}; **^{1}H NMR** (*trans*, 400 MHz, $CDCl_3$): δ 0.88 (t, ^3J=7.1 Hz, 6H, 2 x CH_3), 0.98-1.02 (m, 2H, H_6 and H_7), 1.22-1.50 (m, 12H, 6 x CH_2), 1.98 (qn, $^3J_{3\text{-}2}=^3J_{3\text{-}4}$=7.5 Hz, 2H, H_3), 2.01 (t, $^3J_{5\text{-}6}=^3J_{5\text{-}7}$=3.8 Hz, 1H, H_5), 2.32 (t, $^3J_{2\text{-}3}$=8.1 Hz, 2H, H_2), 3.25 (t, $^3J_{4\text{-}3}$=7.0 Hz, 2H, H_4); **^{13}C NMR** (*trans*, 100 MHz, $CDCl_3$): δ 14.1 (CH_3), 18.0 (CH_2), 22.6 (CH_2), 23.5 (C_6 and C_7), 26.8 (CH_2), 31.8 (C_2), 37.8 (C_5), 47.4 (C_4), 175.6 (C_1); **^{1}H NMR** (*cis*, 400 MHz, $CDCl_3$): δ 0.88 (t, ^3J=7.2 Hz, 6H, 2 x CH_3), 0.91-0.98 (m, 2H, H_6 and H_7), 1.16-1.51 (m, 12H, 6 x CH_2), 1.98 (qn, $^3J_{3\text{-}2}=^3J_{3\text{-}4}$=7.5 Hz, 2H, H_3), 2.31 (t, $^3J_{2\text{-}3}$=8.2 Hz, 2H, H_2), 2.38 (t, $^3J_{5\text{-}6}=^3J_{5\text{-}7}$=7.7 Hz, 1H, H_5), 3.25 (t, $^3J_{4\text{-}3}$=7.0 Hz, 2H, H_4); **^{13}C NMR** (*cis*, 100 MHz, $CDCl_3$): δ 14.1 (CH_3), 18.9 (CH_2), 19.8 (C_6 and C_7), 22.9 (CH_2), 23.4 (CH_2), 31.0 (CH_2), 32.4 (CH_2), 33.4 (C_2), 48.8 (C_4), 178.5 (C_1); **EI-MS** *m/z* (%): 238 (MH^+, 100), 194 ($[M\text{-}C_3H_7]^+$, 25), 180 ($[M\text{-}C_4H_9]^+$, 95), 138 ($[M\text{-}C_7H_{15}]^+$, 13), 124 ($[M\text{-}C_8H_{17}]^+$, 43), 98 (73), 86 (43), 67 ($C_5H_7^+$, 10), 55 (13), 41 (34); **HMRS**: M^+, found 237.20916. $C_{15}H_{27}NO$ requires 237.20925.

1-Bicyclo[4.1.0]hept-7-yl-2-pyrrolidinone 87

exo





endo

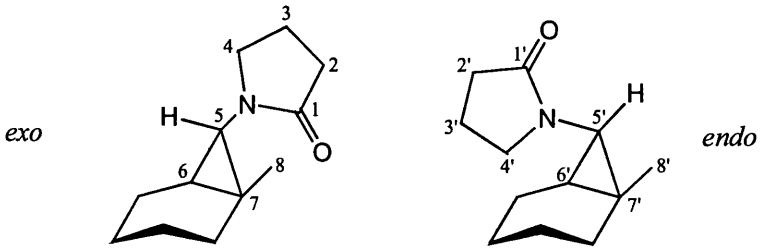
$C_{11}H_{17}NO$ 179.26 $g.mol^{-1}$

A solution of *N*-diethoxymethy-2-pyrrolidinone **78** (0.68 g, 3.65 mmol, 2 eq) in dry diethyl ether (4 mL) was added *via* a motorised syringe pump over 16 h to a vigorously stirred mixture of zinc amalgam (2.39 g, 36.5 mmol, 20 eq), anhydrous zinc chloride (0.50 g, 3.65 mmol, 2 eq), chlorotrimethylsilane (2.32 mL, 18.25 mmol, 10 eq) and freshly distilled cyclohexene (0.15 g, 1.82 mmol, 1 eq) in dry diethyl ether (10.5 mL) under nitrogen at reflux. The mixture was stirred for 6 h and then allowed to cool to room temperature. The reaction was quenched with saturated aqueous $NaHCO_3$ solution (25 mL) and after stirring for 20 min, the mixture was filtered through celite and the

separated zinc washed with diethyl ether (20 mL) and dichloromethane (20 mL). The organic solvents were removed *in vacuo* and the aqueous layer was extracted with diethyl ether (3 x 25 mL). The combined organic extracts were washed with brine (25 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (silica, EtOAc/MeOH 98:2 to 95:5) to give an inseparable mixture of *endo* and *exo* cyclopropanes **87** (0.215 g, 1.2 mmol, 66%, *exo*/*endo*: 10:1 as determined by ^{1}H NMR) as a colourless oil.

R_f (EtOAc/MeOH 95:5) 0.38; **IR** (mixture of *exo* and *endo*, film): ν_{max} 2927 (s), 2853 (s), 1682 (s, C=O), 1418 (s), 1291 (s), 1248 (m) cm^{-1}; **^{1}H NMR** (*exo*, 500 MHz, C_6D_6): δ0.93-1.00 (m, 2H), 1.03-1.11 (m, 4H), 1.21 (qn, $^3J_{3\text{-}2}$=$^3J_{3\text{-}4}$=7.5 Hz, 2H, H_3), 1.65-1.79 (m, 4H), 1.97 (t, $^3J_{2\text{-}3}$=8.0 Hz, 2H, H_2), 2.22 (t, $^3J_{5\text{-}6}$=$^3J_{5\text{-}7}$=3.7 Hz, 1H, H_5), 2.57 (t, $^3J_{4\text{-}3}$=7.0 Hz, 2H, H_4); **^{13}C NMR** (*exo*, 125 MHz, C_6D_6): δ 17.2 (C_6 and C_7), 18.1 (C_3), 21.6 (2 x CH_2), 22.7 (2 x CH_2), 31.6 (C_2), 36.9 (C_5), 46.4 (C_4), 174.4 (C_1); **^{1}H NMR** (*endo*, 500 MHz, C_6D_6): δ0.87-0.92 (m, 2H, H_6 and H_7), 0.93-1.13 (m, 4H), 1.29 (qn, $^3J_{3\text{-}2}$=$^3J_{3\text{-}4}$=7.5 Hz, 2H, H_3), 1.65-1.79 (m, 4H); 1.93 (t, $^3J_{2\text{-}3}$=7.9 Hz, 2H, H_2), 2.04 (t, $^3J_{5\text{-}6}$=$^3J_{5\text{-}7}$=7.7 Hz, 1H, H_5), 2.79 (t, $^3J_{4\text{-}3}$=6.9 Hz, 2H, H_4); **^{13}C NMR** (*endo*, 125 MHz, C_6D_6): δ 13.0 (C_6 and C_7), 18.9 (C_3), 20.2 (2 x CH_2), 22.5 (2 x CH_2), 30.9 (C_2), 34.0 (C_5), 48.0 (C_4), 176.7 (C_1); **EI-MS** *m/z* (%): 179 (M^+, 100), 150 (32), 136 (15), 124 (20), 108 (10), 98 (32), 94 (30), 79 (19), 72 (30), 59 (57), 55 (48); **HMRS**: M^+, found 179.13102. $C_{11}H_{17}NO$ requires 179.1310.

1-(1-Methylbicyclo[4.1.0]hept-7-yl)-2-pyrrolidinone 88



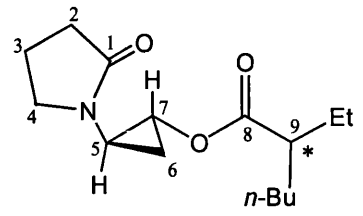
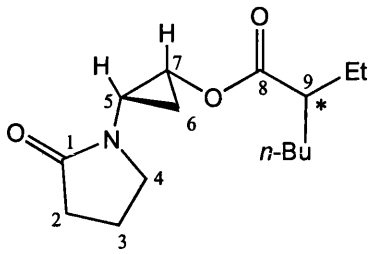
$C_{12}H_{19}NO$ 193.29 g.mol^{-1}

A solution of *N*-diethoxymethy-2-pyrrolidinone **78** (0.58 g, 3.12 mmol, 2 eq) in dry diethyl ether (4 mL) was added *via* a motorised syringe pump over 16 h to a vigorously stirred mixture of zinc amalgam (2.04 g, 31.2 mmol, 20 eq), anhydrous zinc chloride

(0.425 g, 3.12 mmol, 2 eq), chlorotrimethylsilane (1.98 mL, 15.6 mmol, 10 eq) and 1-methylcyclohex-1-ene (0.15 g, 1.56 mmol, 1 eq) in dry diethyl ether (8.5 mL) under nitrogen at reflux. The mixture was stirred for 6 h and then allowed to cool to room temperature. The reaction was quenched with saturated aqueous $NaHCO_3$ solution (25 mL) and after stirring for 20 min, the mixture was filtered through celite and the separated zinc washed with diethyl ether (20 mL) and dichloromethane (20 mL). The organic solvents were removed *in vacuo* and the aqueous layer was extracted with diethyl ether (3 x 25 mL). The combined organic extracts were washed with brine (25 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (silica, EtOAc/MeOH 98:2) to give an inseparable mixture of *endo* and *exo* cyclopropanes **88** (0.189 g, 0.98 mmol, 63%, *exo/endo*: 1.3:1 as determined by ^1H NMR) as a colourless oil.

R_f (EtOAc) 0.33; **IR** (mixture of *exo* and *endo*, film): ν_{max} 2929 (s), 2861 (m), 1693 (s, C=O), 1492 (w), 1412 (m), 1286 (m), 1090 (w) cm^{-1}; **^1H NMR** (mixture of *exo* and *endo*, 500 MHz, C_6D_6): δ 0.73 (dt, ^3J=2.6 Hz, ^3J=$^3J_{6'\text{-}5'}$=7.9 Hz, 1H, $H_{6'}$), 0.90 (ddt, ^3J=1.7 Hz, $^3J_{6\text{-}5}$=4.1 Hz, ^3J=7.5 Hz, 1H, H_6), 0.96-1.22 (m, 14H), 1.27-1.35 (m, 4H, H_3 and $H_{3'}$), 1.47-1.66 (m, 4H), 1.75-1.90 (m, 5H), 1.91-1.96 (m, 2H, $H_{2'}$), 1.98-2.03 (m, 2H, H_2), 2.09 (d, $^3J_{5\text{-}6}$=4.2 Hz, 1H, H_5), 2.66 (td, $^3J_{4\text{-}3}$=7.0 Hz, ^2J=9.3 Hz, 1H, H_4), 2.68 (td, $^3J_{4\text{-}3}$=7.0 Hz, ^2J=9.3 Hz, 1H, H_4), 2.78 (td, $^3J_{4'\text{-}3'}$=7.0 Hz, ^2J=9.3 Hz, 1H, $H_{4'}$), 2.80 (td, $^3J_{4'\text{-}3'}$=6.3 Hz, ^2J=9.3 Hz, 1H, $H_{4'}$); **^{13}C NMR** (mixture of *exo* and *endo*, 125 MHz, C_6D_6): δ 18.2 (C_6), 18.6 (C_3), 19.0 ($C_{3'}$), 20.4 (CH_2), 21.6 (CH_2), 21.7 ($C_{7'}$ and C_8), 21.9 (CH_2), 22.1 ($C_{6'}$), 22.3 (CH_2), 22.4 (CH_2), 23.2 (CH_2), 23.5 (C_7), 27.8 (CH_2), 28.0 ($C_{8'}$), 30.5 ($C_{2'}$), 31.0 (CH_2), 31.4 (C_2), 41.2 ($C_{5'}$), 41.4 (C_5), 47.9 (C_4), 48.1 ($C_{4'}$), 175.2 ($C_{1'}$), 176.6 (C_1); **EI-MS** *m/z* (%): 193 (M^+, 67), 178 ($[M\text{-}CH_3]^+$, 45), 164 ($[M\text{-}C_2H_5]^+$, 20), 150 ($[M\text{-}C_3H_7]^+$, 15), 124 (10), 108 (83), 98 (53), 93 (55), 86 (100), 79 (18), 55 (14). **HMRS**: M^+, found 193.14610. $C_{12}H_{19}NO$ requires 193.14655.

2-Ethylhexyl-[2-(2-oxopyrrolidin-1-yl)-cyclopropyl] carboxylate 90

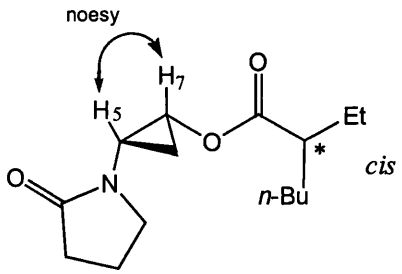
trans   *cis*

$C_{15}H_{25}NO_3$ 267.37 g.mol^{-1}

A solution of *N*-diethoxymethy-2-pyrrolidinone **78** (0.44 g, 2.35 mmol, 2 eq) in dry diethyl ether (3 mL) was added *via* a motorised syringe pump over 4 h to a vigorously stirred mixture of zinc amalgam (1.54 g, 23.5 mmol, 20 eq), zinc chloride (1M solution in diethyl ether, 2.35 mL, 2.35 mmol, 2 eq), chlorotrimethylsilane (1.49 mL, 11.7 mmol, 10 eq) and vinyl 2-ethylhexanoate (0.2 g, 1.17 mmol, 1 eq) in dry diethyl ether (4 mL) under nitrogen at reflux. The reaction mixture was cooled to room temperature and then stirred for 12 h. The reaction was quenched with saturated aqueous $NaHCO_3$ solution (20 mL) and after stirring for 20 min, the mixture was filtered through celite and the separated zinc washed with diethyl ether (20 mL) and dichloromethane (20 mL). The organic solvents were removed *in vacuo* and the aqueous layer was extracted with diethyl ether (3 x 20 mL). The combined organic extracts were washed with brine (20 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (silica, EtOAc/P.E. 30-40°C 4:1 to 8.5:1.5) to give a diastereomeric mixture of *cis* and *trans* cyclopropanes **90** (0.179 g, 0.67 mmol, 57%, *trans*/*cis*: 2:1 as determined by ^{1}H NMR) as a colourless oil.

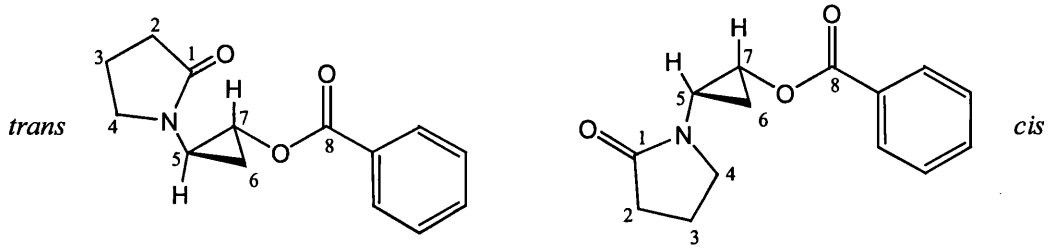
R_f (EtOAc/P.E. 40-60°C 4:1) 0.34; **IR** (diastereomeric mixture of *trans* and *cis*, film): ν_{max} 2961 (s), 2934 (s), 2875 (m), 2862 (m), 1741 (s, C=O), 1698 (s, C=O), 1460 (s), 1420 (s), 1296 (s), 1208 (m), 1170 (s), 1150 (s) cm^{-1}; **^{1}H NMR** (diastereomeric mixture of *trans*, 500 MHz, $CDCl_3$): δ 0.74 (t, ^3J=7.2 Hz, 12H, 4 x CH_3), 1.05-1.21 (m, 10H, H_6 and 4 x CH_2), 1.22 (dt, $^3J_{6\text{-}5}$=5.5 Hz, ^2J=$^3J_{6\text{-}7}$=7.6 Hz, 2H, H_6), 1.26-1.51 (m, 8H, 4 x CH_2), 1.80-1.93 (m, 4H, H_3), 2.10 (tt, ^3J=5.5 Hz, ^3J =8.8 Hz, 2H, H_9), 2.22 (t, $^3J_{2\text{-}3}$=8.3 Hz, 4H, H_2), 2.57 (ddd, $^3J_{5\text{-}7}$=1.8 Hz, $^3J_{5\text{-}6}$=5.3 Hz, $^3J_{5\text{-}6}$=7.4 Hz, 2H, H_5), 3.26-3.38 (m, 4H, H_4), 3.97 (ddd, $^3J_{7\text{-}5}$=1.8 Hz, $^3J_{7\text{-}6}$=4.4 Hz, $^3J_{7\text{-}6}$=7.4 Hz, 2H, H_7); **^{13}C NMR**

(diastereomeric mixture of *trans*, 125 MHz, $CDCl_3$): δ 11.5 (CH_3), 13.6 (C_6 and CH_3), 17.8 (C_3), 22.3 (2 x CH_2), 25.0 (CH_2), 29.2 (2 x CH_2), 31.1 (2 x C_5), 31.3 (C_2 and CH_2), 46.6 (2 x C_9), 47.0 (C_4), 51.7 (C_7), 175.8 (C=O), 176.2 (C=O), 176.7 (C=O); **^{1}H NMR** (diastereomeric mixture of *cis*, 300 MHz, $CDCl_3$): δ 0.83 (t, ^3J=7.3 Hz, 12H, 4 x CH_3), 1.13-1.57 (m, 20H), 1.89-2.01 (m, 4H, H_3), 2.19 (tt, ^3J=5.6 Hz, ^3J =8.2 Hz, 2H, H_9), 2.34 (t, $^3J_{2\text{-}3}$=8.1 Hz, 4H, H_2), 2.65-2.70 (m, 2H, H_5), 3.26-3.43 (m, 4H, H_4), 4.14 (dt, ^3J=4.1 Hz, ^3J=7.1 Hz, 1H, H_7), 4.15 (dt, ^3J=4.1 Hz, ^3J=7.1 Hz, 1H, H_7).



^{13}C NMR (diastereomeric mixture of *cis*, 125 MHz, $CDCl_3$): δ 11.2 (2 x C_6), 11.6 (CH_3), 13.8 (CH_3), 18.3 (C_3), 22.5 (2 x CH_2), 25.0 (CH_2), 25.3 (CH_2), 28.7 (C_5), 29.4 (2 x CH_2), 31.3 (CH_2), 31.5 (CH_2), 31.6 (CH_2), 47.0 (2 x C_9), 48.1 (C_4), 49.7 (C_7), 176.3 (2 x C=O), 176.5 (C=O); **EI-MS** *m/z* (%): 268 (MH^+, 49), 140 (99), 124 (32), 112 (87), 99 ($C_7H_{15}^+$, 28), 84 (11), 69 (42), 57 ($C_4H_9^+$, 100), 41 (73); **HMRS**: MH^+, found 268.19116. $C_{15}H_{26}NO_3$ requires 268.19124.

[2-(2-oxopyrrolidin-1-yl)-cyclopropyl] benzoate 92



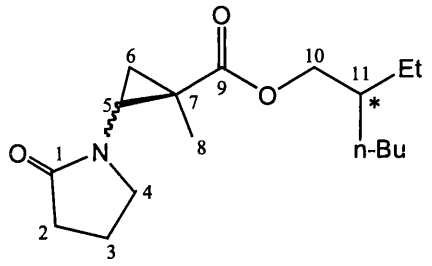
$C_{14}H_{15}NO_3$ 245.27 g.mol^{-1}

A solution of *N*-diethoxymethy-2-pyrrolidinone **78** (0.50 g, 2.70 mmol, 2 eq) in dry diethyl ether (2 mL) was added *via* a motorised syringe pump over 4.5 h to a vigorously stirred mixture of zinc amalgam (1.76 g, 27.0 mmol, 20 eq), zinc chloride (1M solution in diethyl ether, 2.70 mL, 2.70 mmol, 2 eq), chlorotrimethylsilane (1.71 mL, 13.5 mmol,

10 eq) and vinyl benzoate (0.20 g, 1.35 mmol, 1 eq) in dry diethyl ether (5 mL) under nitrogen at reflux. The reaction mixture was cooled to room temperature and then stirred for 12 h. The reaction was quenched with saturated aqueous $NaHCO_3$ solution (20 mL) and after stirring for 20 min, the mixture was filtered through celite and the separated zinc washed with diethyl ether (20 mL) and dichloromethane (20 mL). The organic solvents were removed *in vacuo* and the aqueous layer was extracted with diethyl ether (3 x 20 mL). The combined organic extracts were washed with brine (20 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (silica, EtOAc/MeOH 96:4) to give a diastereomeric mixture of *cis* and *trans* cyclopropanes **92** (0.185 g, 0.75 mmol, 56%, *trans/cis*: 2:1 as determined by ^{1}H NMR) as a colourless oil.

R_f (EtOAc) 0.23; **IR** (mixture of *trans* and *cis*, film): ν_{max} 2961 (m), 1726 (s, C=O), 1689 (s, C=O), 1615 (w, C=C), 1452 (m), 1420 (s), 1271 (s), 1178 (m), 1138 (m), 1111 (m), 1070 (m), 1026 (m), 713 (s) cm^{-1}; **^{1}H NMR** (*trans*, 500 MHz, $CDCl_3$): δ 1.40-1.43 (m, 2H, H_6), 1.89-1.98 (m, 2H, H_3), 2.36 (t, $^3J_{2\text{-}3}$=8.4 Hz, 2H, H_2), 2.80 (ddd, $^3J_{5\text{-}7}$=5.4 Hz, $^3J_{5\text{-}6}$=7.0 Hz, $^3J_{5\text{-}6}$=7.8 Hz, 1H, H_5), 3.33-3.43 (m, 2H, H_4), 4.44 (q, $^3J_{7\text{-}5}$=$^3J_{7\text{-}6}$=5.4 Hz, 1H, H_7), 7.38-7.42 (m, 2H, H_{arom}), 7.51-7.56 (m, 1H, H_{arom}), 7.90-7.94 (m, 2H, H_{arom}); **^{13}C NMR** (*trans*, 125 MHz, $CDCl_3$): δ 11.2 (C_6), 18.5 (C_3), 29.0 (C_5), 31.5 (C_2), 48.2 (C_4), 50.6 (C_7), 128.4 (CH), 129.3 (CH and C_q), 133.2 (CH), 166.8 (C_8), 176.7 (C_1); **^{1}H NMR** (*cis*, 500 MHz, $CDCl_3$): δ 1.44-1.48 (m, 2H, H_6), 1.95-2.07 (m, 2H, H_3), 2.37 (t, $^3J_{2\text{-}3}$=8.4 Hz, 2H, H_2), 2.85 (ddd, $^3J_{5\text{-}6}$=1.8 Hz, $^3J_{5\text{-}7}$=6.7 Hz, $^3J_{5\text{-}6}$=9.0 Hz, 1H, H_5), 3.45-3.53 (m, 2H, H_4), 4.33 (ddd, $^3J_{7\text{-}6}$=1.8 Hz, $^3J_{7\text{-}6}$=5.4 Hz, $^3J_{7\text{-}5}$=6.5 Hz, 1H, H_7), 7.38-7.42 (m, 2H, H_{arom}), 7.51-7.56 (m, 1H, H_{arom}), 7.90-7.94 (m, 2H, H_{arom}); **^{13}C NMR** (*cis*, 125 MHz, $CDCl_3$): δ 14.0 (C_6), 18.5 (C_3), 31.4 (C_5), 31.6 (C_2), 47.4 (C_4), 52.6 (C_7), 128.4 (CH), 129.3 (C_q), 129.6 (CH), 133.3 (CH), 167.1 (C_8), 176.2 (C_1); **EI-MS** *m/z* (%): 245 (M^+, 74), 216 (24), 162 ($[M+H-C_4H_6NO]^+$, 61), 154 (22), 141 (86), 124 ($[M-Ph-CO_2]^+$, 100), 114 (100), 106 (89), 94 (87), 84 (90), 77 (Ph^+, 86); **HMRS**: MH^+, found 245.10578. $C_{14}H_{15}NO_3$ requires 245.10519.

2-Ethylhexyl-[1-methyl-2-(2-oxopyrrolidin-1-yl)-cyclopropyl] carboxylate 94



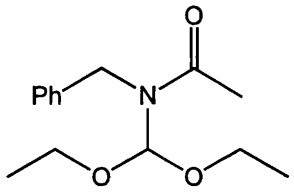
$C_{17}H_{29}NO_3$ 295.42 g.mol^{-1}

A solution of *N*-diethoxymethy-2-pyrrolidinone **78** (0.375 g, 2.02 mmol, 2 eq) in dry diethyl ether (3 mL) was added *via* a motorised syringe pump over 12 h to a vigorously stirred mixture of zinc amalgam (1.32 g, 20.2 mmol, 20 eq), zinc chloride (1M solution in diethyl ether, 2 mL, 2.0 mmol, 2 eq), chlorotrimethylsilane (1.28 mL, 10.1 mmol, 10 eq) and 2-ethylhexyl methacrylate (0.2 g, 1.01 mmol, 1 eq) in dry diethyl ether (3 mL) under nitrogen at reflux. The mixture was stirred for 6 h and then allowed to cool to room temperature. The reaction was quenched with saturated aqueous $NaHCO_3$ solution (20 mL) and after stirring for 20 min, the mixture was filtered through celite and the separated zinc washed with diethyl ether (20 mL) and dichloromethane (20 mL). The organic solvents were removed *in vacuo* and the aqueous layer was extracted with diethyl ether (3 x 20 mL). The combined organic extracts were washed with brine (20 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (silica, EtOAc/P.E. 30-40°C 7:3 to 4:1) to give an inseparable diastereomeric mixture of *cis* and *trans* cyclopropanes **94** (26 mg, 0.09 mmol, 9%, *trans*/*cis* 1:1 as determined by ^{1}H NMR) as a colourless oil.

R_f (EtOAc/P.E. 30-40°C 4:1) 0.43; **IR** (diastereomeric mixture of *trans* and *cis*, film): ν_{max} 2975 (s), 2931 (s), 2865 (m), 1700 (s, C=O), 1459 (w), 1419 (w), 1297 (w), 1170 (w), 913 (w), 732 (m) cm^{-1}; **^{1}H NMR** (diastereomeric mixture of *trans* and *cis*, 500 MHz, $CDCl_3$): δ 0.85 (t, ^3J=7.0 Hz, 24H, 8 x CH_3), 1.04 (t, $^3J_{6\text{-}5}$=^2J=6.8 Hz, 2H, H_6), 1.18-1.35 (m, 46H, $H_{6'}$, H_8, $H_{8'}$, 16 x CH_2), 1.49-1.56 (m, 4H, H_{11} and $H_{11'}$), 1.63 (dd, J=5.8 Hz, J=8.7 Hz, 2H, $H_{6'}$), 1.67-1.71 (m, 2H, H_6), 1.89-2.03 (m, 8H, H_3 and $H_{3'}$), 2.25-2.31 (m, 4H, CH_2), 2.37 (t, ^3J=8.4 Hz, 4H, CH_2), 2.69 (t, $^3J_{5\text{-}6}$=6.8 Hz, 2H, H_5), 2.99 (dd, ^3J=5.7 Hz, ^3J=8.5 Hz, 2H, $H_{5'}$), 3.20-3.36 (m, 6H), 3.49 (td, ^3J=7.5 Hz,

^{2}J=8.9 Hz, 2H), 3.85-3.98 (m, 8H, H_{10} and $H_{10'}$); **^{13}C NMR** (diastereomeric mixture of *trans* and *cis*, 125 MHz, $CDCl_3$): δ 10.9 (2 x CH_3), 11.0 (CH_3), 13.3 (CH_3), 18.3 (CH_2), 18.4 (CH_2), 19.2 (2 x CH_3), 20.5 (C_6), 20.8 ($C_{6'}$), 22.9 (CH_2), 23.7 (2 x CH_2), 23.8 (CH_2), 24.3 (CH_2), 26.2 (C_7 and $C_{7'}$), 29.3 (CH_2), 30.3 (CH_2), 30.4 (CH_2), 38.6 (C_{11} and $C_{11'}$), 38.7 ($C_{5'}$), 40.4 (C_5), 48.0 (CH_2), 48.9 (CH_2), 67.1 (CH_2), 67.2 (2 x CH_2), 67.3 (CH_2), 172.2 (C=O), 174.0 (C=O), 176.4 (C=O), 176.5 (C=O); **EI-MS** *m/z* (%): 296 (MH^+, 100), 183 (60), 165 (65), 138 (85), 98 (64), 71 ($C_5H_{11}^+$, 14), 57 ($C_4H_9^+$, 27), 41 (49); **HMRS**: MH^+, found 296.22254. $C_{17}H_{30}NO_3$ requires 296.22234.

_N_-Benzyl-_N_-diethoxymethylacetamide 96



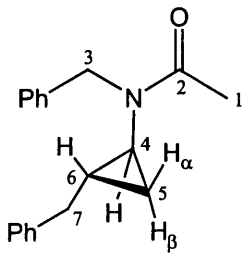
$C_{14}H_{21}NO_3$ 251.33 g.mol^{-1}

A mixture of *N*-benzylacetamide (1.0 g, 6.7 mmol, 1 eq), aluminium chloride (0.13 g, 1.0 mmol, 0.15 eq) and triethyl orthoformate (22 mL, 0.13 mol, 20 eq) was heated at 155°C for 72 h. The reaction mixture was allowed to cool to room temperature and then quenched with saturated aqueous $NaHCO_3$ solution (25 mL). The aqueous phase was extracted with diethyl ether (50 mL then 2 x 25 mL) and the combined organic extracts were washed with brine (25 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (silica, P.E. 40-60°C/EtOAc 4:1 to 7:3) to give the *title compound* **96** (0.3 g, 1.19 mmol, 18%, 7:3 mixture of rotamers at 353 K) as a yellow oil.

R_f (P.E. 30-40°C/EtOAc 7:3) 0.35; **IR** (film): ν_{max} 2978 (m), 2933 (w), 1670 (s, C=O), 1497 (w), 1103 (s), 1063 (s), 974 (m), 733 (w), 700 (s) cm^{-1}; **^{1}H NMR** (400 MHz, 353 K, DMSO): δ 1.10 (t, ^{3}J=7.1 Hz, 6H, CH_2CH_3), 2.05 (s, 0.7 x 3H, $COCH_3$), 2.98 (s, 0.3 x 3H, $COCH_3$), 3.37-3.63 (m, 4H, CH_2CH_3), 4.41 (s, 0.3 x 2H, $PhCH_2N$), 4.50 (s, 0.7 x 2H, $PhCH_2N$), 5.58 (br s, 0.3 x 1H, OCHO), 6.00 (br s, 0.7 x 1H, OCHO), 7.16-7.35 (m, 5H, H_{arom}); **^{13}C NMR** (major rotamer, 100 MHz, 353 K, DMSO): δ 14.0 (CH_3), 21.4 ($COCH_3$), 43.7 ($PhCH_2N$), 61.2 (CH_2CH_3), 102.2 (OCHO), 125.8 (CH), 126.7 (CH),

127.3 (CH), 138.9 (C_q), 169.0 (C=O); **CI(methane)-MS** *m/z* (%): 252 (MH^+, 3), 206 ($[M-OC_2H_5]^+$, 62), 150 (100), 103 (61), 91 (Bn^+, 68); **HMRS**: MH^+, found 252.16019. $C_{14}H_{22}NO_3$ requires 252.15997.

_N_-Benzyl-_N_-(2-benzylcyclopropyl)-acetamide 97



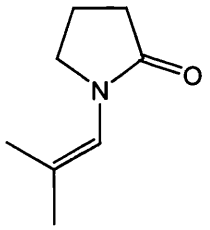
$C_{19}H_{21}NO$ 279.38 g.mol^{-1}

A solution of *N*-benzyl-*N*-diethoxymethylacetamide **96** (0.80 g, 3.18 mmol, 2 eq) in dry diethyl ether (3 mL) was added *via* a motorised syringe pump over 6 h to a vigorously stirred mixture of zinc amalgam (2.08 g, 31.8 mmol, 20 eq), zinc chloride (1M solution in diethyl ether, 3.18 mL, 3.18 mmol, 2 eq), chlorotrimethylsilane (2.02 mL, 15.9 mmol, 10 eq) and allylbenzene (0.188 g, 1.59 mmol, 1 eq) in dry diethyl ether (6.5 mL) under nitrogen at reflux. The mixture was stirred for 16 h and then allowed to cool to room temperature. The reaction was quenched with saturated aqueous $NaHCO_3$ solution (30 mL) and after stirring for 20 min, the mixture was filtered through celite and the separated zinc washed with diethyl ether (20 mL) and dichloromethane (20 mL). The organic solvents were removed *in vacuo* and the aqueous layer was extracted with diethyl ether (3 x 30 mL). The combined organic extracts were washed with brine (30 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (silica, isohexane/EtOAc 3:2 to 5.5:4.5) to give an inseparable mixture of *cis* and *trans* cyclopropanes **97** (61 mg, 0.22 mmol, 14%, *trans*/*cis*: 13.5:1 as determined by ^{1}H NMR) as a colourless oil.

R_f (P.E. 40-60°C/EtOAc 3:2) 0.3; **IR** (mixture of *trans* and *cis*, film): ν_{max} 3026 (w), 2924 (w), 1655 (s, C=O), 1603 (w, C=C), 1495 (w), 1452 (w), 1398 (m), 1358 (w), 1294 (w), 725 (w), 698 (m) cm^{-1}; **^{1}H NMR** (*trans*, 500 MHz, $CDCl_3$): δ 0.78 (ddd, $^2J_{5\beta\text{-}5\alpha}$=5.4 Hz, $^3J_{5\beta\text{-}6}$=6.2 Hz, $^3J_{5\beta\text{-}4}$=7.1 Hz, 1H, $H_{5\beta}$), 0.95 (ddd, $^3J_{5\alpha\text{-}4}$=4.0 Hz,

$^2J_{5\alpha\text{-}5\beta}$=5.5 Hz, $^3J_{5\alpha\text{-}6}$=9.5 Hz, 1H, $H_{5\alpha}$), 1.37 (dtdd, $^3J_{6\text{-}4}$=3.5 Hz, $^3J_{6\text{-}5\beta}$=$^3J_{6\text{-}7}$=6.1 Hz, $^3J_{6\text{-}7}$=7.5 Hz, $^3J_{6\text{-}5\alpha}$=9.4 Hz, 1H, H_6), 2.16 (s, 3H, H_1), 2.33-2.44 (m, 1H, H_4), 2.42 (dd, $^3J_{7\text{-}6}$=7.5 Hz, ^2J=14.5 Hz, 1H, H_7), 2.66 (dd, $^3J_{7\text{-}6}$=6.1 Hz, ^2J=14.5 Hz, 1H, H_7), 4.45 (d, ^2J=14.8 Hz, 1H, H_3), 4.53 (d, ^2J=14.8 Hz, 1H, H_3), 7.08-7.12 (m, 4H, H_{arom}), 7.19-7.31 (m, 6H, H_{arom}); **^{13}C NMR** (*trans*, 125 MHz, $CDCl_3$): δ 15.9 (C_5), 22.7 (C_1), 23.3 (C_6), 36.8 (C_4), 37.7 (C_7), 49.6 (C_3), 126.3 (CH), 126.9 (CH), 128.4 (CH), 128.5 (CH), 138.1 (C_q), 139.7 (C_q), 173.3 (C_2); **EI-MS** *m/z* (%): 279 (M^+, 65), 264 ($[M\text{-}CH_3]^+$, 37), 236 ($[M\text{-}COCH_3]^+$, 100), 188 ($[M\text{-}Bn]^+$, 100), 148 (74), 131 ($C_{10}H_{11}^+$, 66), 106 (52), 91 (Bn^+, 82), 77 (Ph^+, 24); **HMRS**: M^+, found 279.16205. $C_{19}H_{21}NO$ requires 279.16231.

1-(2-Methylpropenyl)-2-pyrrolidinone 99



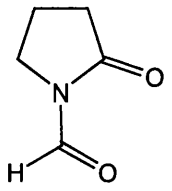
$C_8H_{13}NO$ 139.20 g.mol^{-1}

The *title compound* was prepared by a literature method.[131] A mixture of 2-pyrrolidinone (8.51 g, 10 mmol, 1 eq), isobutylaldehyde (13.5 mL, 0.15 mmol, 1.5 eq) and catalytic amount of *p*-toluenesulfonic acid (~20 mg) in toluene (150 mL) was heated at reflux for 7 h in conjunction with a Dean-Stark apparatus for water removal. The reaction mixture was cooled to room temperature and then washed with saturated aqueous $NaHCO_3$ solution (100 mL) and water (100 mL). The combined aqueous layers were extracted with diethyl ether (100 mL) and the combined organic extracts were then dried (Na_2SO_4), filtered and concentrated *in vacuo* to give the *enamide* **99** (9.0 g, 6.46 mmol, 65%) as a yellow oil which was used without further purification.

IR (film): ν_{max} 2991 (w), 2960 (w), 2885 (w), 1697 (s, C=O), 1672 (s, C=C), 1406 (m), 1379 (w), 1292 (s) cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$): δ 1.63 (s, 3H, CH_3), 1.70 (s, 3H, CH_3), 1.97-2.03 (m, 2H, $CH_2CH_2CH_2$), 2.36 (t, ^3J=8.1 Hz, 2H, CH_2CO), 3.53 (t, ^3J=7.1 Hz, 2H, CH_2N), 5.86 (s, 1H, NCH=); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 18.3

($CH_2CH_2CH_2$), 18.7 (CH_3), 23.0 (CH_3), 30.6 (CH_2CO), 49.2 (CH_2N), 119.4 (NCH=), 128.4 ($=C(CH_3)_2$), 174.5 (C=O).

_N_-Formyl-2-pyrrolidinone 100

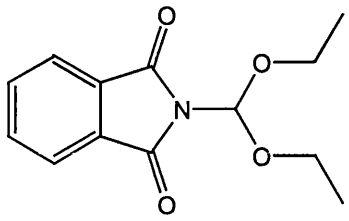


$C_5H_7NO_2$ 113.12 g.mol^{-1}

Ozone was bubbled through a solution of crude enamide **99** (9 g, 64.65 mmol, 1 eq) in dichloromethane (500 mL) at –78°C. When the reaction mixture turned blue (approximately after 2.5 h of reaction), ozone addition was stopped and nitrogen was passed through the solution until the blue colour was discharged. Dimethylsulfide (9.5 mL, 0.13 mol, 2 eq) was added and the mixture was allowed to warm to room temperature. After 18 h of stirring, the reaction mixture was washed with water (2 x 150 mL) and then dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (silica, P.E. 30-40°C/EtOAc 3:2 to 2:3) to give the *title compound* **100** (4.01 g, 35.45 mmol, 55%) as a yellow oil.

***R*$_f$** (P.E. 40-60°C/EtOAc 1:1) 0.28; **IR** (film): ν_{max} 2985 (w), 2968 (w), 2904 (w), 1751 (s, C=O), 1695 (s, C=O), 1396 (m), 1352 (s), 1325 (w), 1301 (m), 1244 (m), 1220 (m), 1018 (w), 790 (w) cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$): δ 2.04-2.16 (m, 2H, $CH_2CH_2CH_2$), 2.57 (t, ^3J=8.0 Hz, 2H, CH_2CO), 3.71 (t, ^3J=7.1 Hz, 2H, CH_2N), 9.08 (s, 1H, CHO); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 17.8 ($CH_2CH_2CH_2$), 32.1 (CH_2CO), 42.0 (CH_2N), 160.2 (CHO), 176.6 (C=O); **CI(ammonia)-MS** *m/z* (%): 112 ([M-H]$^+$, 100), 83 (24), 55 (25); **HMRS**: (M-H)$^+$, found 112.03977. $C_5H_6NO_2$ requires 112.03985.

_N_-Diethoxymethylphthalimide 101

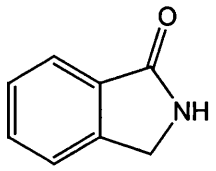


$C_{13}H_{15}NO_4$ 249.26 g.mol^{-1}

A mixture of phthalimide (3.0 g, 20.4 mmol, 1 eq), aluminium chloride (0.3 g, 2.24 mmol, 0.11 eq) and triethyl orthoformate (67 mL, 0.41 mol, 20 eq) was heated at 155°C for 20 h. The reaction mixture was cooled to room temperature and then quenched with saturated aqueous $NaHCO_3$ solution (40 mL). The aqueous phase was extracted with diethyl ether (60 mL then 40 mL) and the combined organic extracts were dried (Na_2SO_4), filtered and concentrated *in vacuo*. The resulting solid was triturated in isopropanol, filtered, washed with isopropanol (10 mL), dried at 50°C *in vacuo* for 4 h to give the *title compound* **101** (3.19 g, 12.8 mmol, 63%) as a white solid.

Mp 73-74°C (lit.,[132] 73°C); R_f (P.E. 40-60°C/EtOAc 1:1) 0.59; **IR** (film): ν_{max} 2977 (w), 1774 (m), 1720 (s), 1694 (w), 1469 (w), 1370 (m), 1348 (m), 1328 (m), 1140 (m), 1110 (m), 1070 (m), 911 (m), 718 (m) cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$): δ 1.25 (t, ^3J=7.1 Hz, 6H, CH_3), 3.62 (qd, ^3J=7.1 Hz, ^2J=9.4 Hz, 2H, CH_2), 3.77 (qd, ^3J=7.1 Hz, ^2J=9.4 Hz, 2H, CH_2), 6.09 (s, 1H, OCHO), 7.68-7.77 (m, 2H, H_{arom}), 7.82-7.90 (m, 2H, H_{arom}); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 14.8 (CH_3), 63.4 (CH_2), 99.8 (OCHO), 123.6 (CH), 131.7 (C_q), 134.3 (CH), 166.6 (C=O); **CI(ammonia)-MS** *m/z* (%): 249 (M^+, 100), 175 ([M-OC_2H_5-C_2H_5]$^+$, 56), 147 (78); **HMRS**: M^+, found 249.09952. $C_{13}H_{15}NO_4$ requires 249.1001.

2,3-Dihydro-1-isoindolinone 105

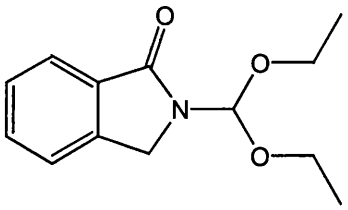


C_8H_7NO 133.15 g.mol^{-1}

The *title compound* was prepared by a literature method.[133] Tin powder (41.7 g, 0.35 mol, 2.6 eq) was added to a vigorously stirred suspension of phthalimide (20 g, 0.136 mol, 1 eq) in a mixture of glacial acetic acid (100 mL) and concentrated hydrochloric acid (50 mL). The reaction mixture was heated at reflux for 2 h and then filtered hot. The filtrate was concentrated *in vacuo* and the residue partitioned between dichloromethane (300 mL) and water (150 mL). The organic layer was separated and the aqueous layer extracted with dichloromethane (2 x 50 mL). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude product was purified twice by flash column chromatography (silica, EtOAc) and then triturated in toluene to give the *title compound* **105** (4.2 g, 31.5 mmol, 23%) as a white solid.

Mp 149-150°C (lit.,[133] 150-151°C); R_f (EtOAc) 0.20; **IR** (CH_2Cl_2): ν_{max} 3214 (br s, NH), 1658 (s, C=O), 1471 (m), 1450 (m), 1361 (w), 764 (s), 749 (s), 726 (s) cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 4.48 (s, 2H, CH_2), 7.18 (br s, 1H, NH), 7.47-7.60 (m, 4H, H_{arom}); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 45.8 (CH_2), 123.2 (CH), 123.6 (CH), 128.0 (CH), 131.7 (CH), 132.6 (C_q), 143.7 (C_q), 172.6 (C=O).

2-Diethoxymethyl-2,3-dihydro-1-isoindolinone 106



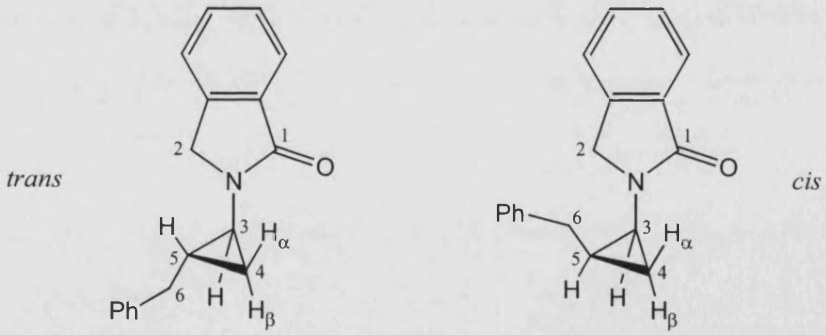
$C_{13}H_{17}NO_3$ 235.28 g.mol^{-1}

A mixture of 1-isoindolinone **105** (4.0 g, 30.04 mmol, 1 eq), aluminium chloride (0.44 g, 3.3 mmol, 0.11 eq) and triethyl orthoformate (100 mL, 0.61 mol, 20 eq) was heated at

155°C for 20 h. The reaction mixture was cooled to room temperature and then quenched with saturated aqueous $NaHCO_3$ solution (100 mL). The aqueous phase was extracted with diethyl ether (2 x 150 mL then 100 mL) and the combined organic extracts were dried (Na_2SO_4), filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (silica, isohexane/EtOAc 1:1) to give the *title compound* **106** (6.58 g, 27.97 mmol, 93%) as a brown oil.

R_f (isohexane/EtOAc 1:1) 0.51; **IR** (film): ν_{max} 2977 (m), 2932 (w), 1694 (s, C=O), 1620 (w, C=C), 1470 (m), 1452 (w), 1388 (s), 1325 (m), 1302 (m), 1242 (m), 1166 (s), 1099 (s), 1055 (s), 918 (w), 890 (w), 839 (w), 798 (w), 734 (s), 703 (m) cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.25 (t, ^3J=7.0 Hz, 6H, CH_3), 3.57 (qd, ^3J=7.0 Hz, ^2J=9.5 Hz, 2H, CH_2CH_3), 3.74 (qd, ^3J=7.0 Hz, ^2J=9.5 Hz, 2H, CH_2CH_3), 4.49 (s, 2H, CH_2N), 6.23 (s, 1H, OCHO), 7.45-7.51 (m, 2H, H_{arom}), 7.58 (t, ^3J=7.5 Hz, 1H, H_{arom}), 7.87 (d, ^3J=7.5 Hz, 1H, H_{arom}); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 14.8 (CH_3), 44.2 (CH_2N), 62.5 (CH_2), 99.2 (OCHO), 123.2 (CH), 124.1 (CH), 128.0 (CH), 132.0 (C_q), 132.1 (CH), 142.0 (C_q), 168.9 (C=O); **CI(methane)-MS** *m/z* (%): 236 (MH^+, 6), 190 ($[M\text{-}OC_2H_5]^+$, 44), 134 (59), 103 (46); **HMRS**: MH^+, found 236.12847. $C_{13}H_{18}NO_3$ requires 236.12866.

2-(2-Benzylcyclopropyl)-2,3-dihydro-1-isoindolinone 107



$C_{18}H_{17}NO$ 263.34 $g.mol^{-1}$

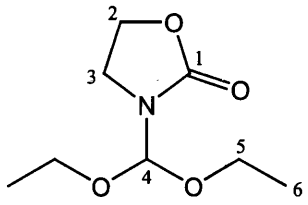
A solution of 2-diethoxymethyl-1-isoindolinone **106** (2.35 g, 10 mmol, 2 eq) in dry diethyl ether (5 mL) was added *via* a motorised syringe pump over 6 h to a vigorously stirred mixture of zinc amalgam (6.6 g, 0.1 mol, 20 eq), zinc chloride (1M solution in diethyl ether, 10 mL, 10 mmol, 2 eq), chlorotrimethylsilane (6.36 mL, 50 mmol, 10 eq) and allylbenzene (0.59 g, 5 mmol, 1 eq) in dry diethyl ether (25 mL) under nitrogen at

reflux. The mixture was stirred for 16 h and then allowed to cool to room temperature. Saturated aqueous $NaHCO_3$ solution (75 mL) and dichloromethane (25 mL) were added to the reaction mixture and after stirring for 20 min, the mixture was filtered through celite and the separated zinc washed with dichloromethane (75 mL). The organic solvents were removed *in vacuo* and the aqueous layer was extracted with dichloromethane (3 x 75 mL). The combined organic extracts were washed with brine (75 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude product was purified twice by flash column chromatography (silica, EtOAc/MeOH 99:1 to 95:5 and then silica, diethyl ether/P.E. 40-60°C 1:1 to 3:1) to give a mixture of *cis* and *trans* cyclopropanes **107** (0.733 g, 2.78 mmol, 56%, *trans/cis*: 6:1 as determined by ^{1}H NMR) as a yellow oil. Trituration of the resulting oil in a mixture of isohexane (5 mL) and ether (1 mL) yields a mixture of *cis* and *trans* cyclopropanes **107** (0.655 g, 2.49 mmol, 50%, *trans/cis*: 15:1 as determined by ^{1}H NMR) as a yellowish solid.

Mp (*trans*) 62-63°C (*i*-Pr_2O); R_f (P.E. 40-60°C/EtOAc 3:7) 0.30; **IR** (mixture of *trans* and *cis*, $CDCl_3$): ν_{max} 3027 (w), 2914 (w), 1685 (s, C=O), 1620 (w, C=C), 1496 (w), 1469 (m), 1453 (m), 1408 (m), 1304 (m), 1214 (w), 1005 (w), 797 (w), 735 (s), 701 (m), 684 (w) cm^{-1}; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 0.93 (dt, $^2J_{4\beta\text{-}4\alpha}$=$^3J_{4\beta\text{-}5}$=6.1 Hz, $^3J_{4\beta\text{-}3}$=7.4 Hz, 1H, $H_{4\beta}$), 1.15 (ddd, $^3J_{4\alpha\text{-}3}$=4.0 Hz, $^2J_{4\alpha\text{-}4\beta}$=5.9 Hz, $^3J_{4\alpha\text{-}5}$=9.6 Hz, 1H, $H_{4\alpha}$), 1.50 (ddtd, $^3J_{5\text{-}3}$=3.4 Hz, $^3J_{5\text{-}4\beta}$=6.4 Hz, $^3J_{5\text{-}6}$=6.9 Hz, $^3J_{5\text{-}4\alpha}$=9.6 Hz, 1H, H_5), 2.67 (dd, $^3J_{6\text{-}5}$=7.1 Hz, ^2J=14.7 Hz, 1H, H_6), 2.80-2.89 (m, 2H, H_3 and H_6), 4.20 (s, 2H, H_2), 7.20-7.53 (m, 8H, H_{arom}), 7.82 (dt, J=1.0 Hz, ^3J=7.5 Hz, 1H, H_{arom}); **^{13}C NMR** (*trans*, 125 MHz, $CDCl_3$): δ 12.8 (C_4), 20.0 (C_5), 31.6 (C_3), 38.2 (C_6), 50.1 (C_2), 122.5 (CH), 123.4 (CH), 126.2 (CH), 127.9 (CH), 128.4 (2 x CH), 131.2 (CH), 133.2 (C_q), 140.6 (C_q), 140.9 (C_q), 169.3 (C_1); **^{1}H NMR** (*cis*, 500 MHz, $CDCl_3$): δ 0.90-0.97 (m, 1H), 1.11-1.19 (m, 2H), 2.24 (dd, $^3J_{6\text{-}5}$=4.9 Hz, ^2J=15.0 Hz, 1H, H_6), 3.03 (dt, $^3J_{3\text{-}4\alpha}$=4.5 Hz, $^3J_{3\text{-}4\beta}$=$^3J_{3\text{-}5}$=7.5 Hz, 1H, H_3), 3.15 (dd, $^3J_{6\text{-}5}$=4.9 Hz, ^2J=15.0 Hz, 1H, H_7), 4.30 (d, ^2J=17.0 Hz, 1H, H_2), 4.32 (d, ^2J=17.0 Hz, 1H, H_2), 7.17-7.57 (m, 8H, H_{arom}), 7.88 (dt, J=1.0 Hz, ^3J=7.4 Hz, 1H, H_{arom}); **^{13}C NMR** (*cis*, 125 MHz, $CDCl_3$): δ 10.6 (C_4), 19.2 (C_5), 30.5 (C_3), 34.0 (C_6), 51.8 (C_2), 122.6 (CH), 123.6 (CH), 125.9 (CH), 128.0 (CH), 128.3 (CH), 128.4 (CH), 131.3 (CH), 133.1 (C_q), 141.1 (C_q), 141.3 (C_q), 170.3 (C_1); **EI-MS** *m/z* (%): 263 (M^+, 13), 222 (8), 172 ($[M\text{-}Bn]^+$, 100), 146 (9), 132 (7), 115

(9), 91 (Bn^+, 29), 77 (Ph^+, 8), 65 (8), 51 (7); **HMRS**: M^+, found 263.13096. $C_{18}H_{17}NO$ requires 263.13101.

_N_-Diethoxymethyl-2-oxazolidinone 108

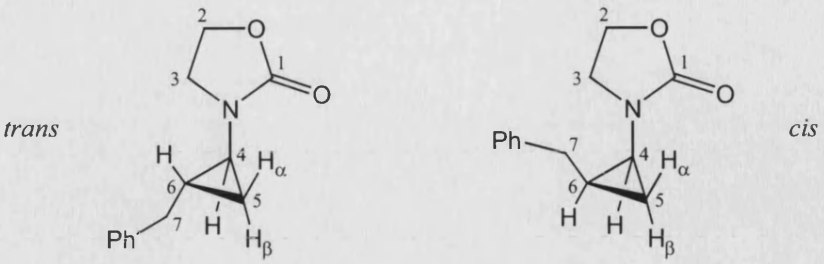


$C_8H_{15}NO_4$ 189.21 g.mol^{-1}

A mixture of 2-oxazolidinone (2.0 g, 22.97 mmol, 1 eq), aluminium chloride (0.31 g, 2.30 mmol, 0.1 eq) and triethyl orthoformate (57 mL, 0.34 mol, 15 eq) was heated at 150°C for 22 h. The reaction mixture was cooled to room temperature and then quenched with saturated aqueous $NaHCO_3$ solution (75 mL). The aqueous phase was extracted with diethyl ether (150 mL then 75 mL) and the combined organic extracts were washed with brine (75 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (silica, isohexane/EtOAc 1:1) to give the *title compound* **108** (2.92 g, 15.4 mmol, 67%) as a yellow oil.

R_f (isohexane/EtOAc 1:1) 0.47; **IR** (film): ν_{max} 2979 (w), 2904 (w), 1747 (s, C=O), 1483 (w), 1416 (m), 1246 (m), 1060 (s), 1037 (m), 975 (m), 897 (w), 763 (s), 704 (s) cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.25 (t, $^3J_{6\text{-}5}$=7.1 Hz, 6H, H_6), 3.53-3.73 (m, 6H, H_3 and H_5), 4.39 (t, $^3J_{2\text{-}3}$=8.2 Hz, 2H, H_2), 5.74 (s, 1H, H_4); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 14.8 (C_6), 38.6 (C_3), 62.6 (C_5), 62.8 (C_2), 101.3 (C_4), 157.4 (C_1); **CI(methane)-MS** *m/z* (%): 190 (MH^+, 2), 144 ($[M\text{-}OC_2H_5]^+$, 100), 116 (12), 103 (100), 75 (14), 44 (16); **HMRS**: MH^+, found 190.10785. $C_8H_{16}NO_4$ requires 190.10793.

3-(2-Benzylcyclopropyl)-2-oxazolidinone 109



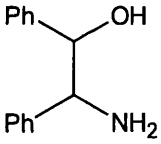
$C_{13}H_{15}NO_2$ 217.27 g.mol^{-1}

A solution of *N*-diethoxymethyl-2-oxazolidinone **108** (0.51 g, 2.71 mmol, 2 eq) in dry diethyl ether (2 mL) was added *via* a motorised syringe pump over 5 h to a vigorously stirred mixture of zinc amalgam (1.77 g, 27.1 mmol, 20 eq), zinc chloride (1M solution in diethyl ether, 2.71 mL, 2.71 mmol, 2 eq), chlorotrimethylsilane (1.71 mL, 13.5 mmol, 10 eq) and allylbenzene (0.16 g, 1.35 mmol, 1 eq) in dry diethyl ether (6 mL) under nitrogen at reflux. The mixture was stirred for 16 h and then allowed to cool to room temperature. The reaction was quenched with saturated aqueous $NaHCO_3$ solution (25 mL) and after stirring for 20 min, the mixture was filtered through celite and the separated zinc washed with diethyl ether (20 mL) and dichloromethane (20 mL). The organic solvents were removed *in vacuo* and the aqueous layer was extracted with diethyl ether (3 x 20 mL). The combined organic extracts were washed with brine (20 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (silica, P.E. 30-40°C/EtOAc 3:2) to give an inseparable mixture of *cis* and *trans* cyclopropanes **109** (0.167 g, 0.77 mmol, 57%, *trans*/*cis*: 15:1 as determined by ^{1}H NMR) as a colourless oil.

R_f (EtOAc/P.E. 40-60°C 3:2) 0.33; **IR** (mixture of *trans* and *cis*, film): ν_{max} 3003 (w), 2915 (w), 1742 (s, C=O), 1604 (w, C=C), 1482 (w), 1419 (w), 1281 (m), 1219 (m), 1129 (w), 1067 (m), 1033 (s), 979 (w), 763 (m), 742 (m), 690 (s) cm^{-1}; **^{1}H NMR** (*trans*, 500 MHz, $CDCl_3$): δ 0.82 (dt, $^2J_{5\beta\text{-}5\alpha}$=$^3J_{5\beta\text{-}6}$=6.1 Hz, $^3J_{5\beta\text{-}4}$=7.1 Hz, 1H, $H_{5\beta}$), 1.03 (ddd, $^3J_{5\alpha\text{-}4}$=3.7 Hz, $^2J_{5\alpha\text{-}5\beta}$=5.9 Hz, $^3J_{5\alpha\text{-}6}$=9.5 Hz, 1H, $H_{5\alpha}$), 1.36 (ddtd, $^3J_{6\text{-}4}$=3.2 Hz, $^3J_{6\text{-}5\beta}$=6.2 Hz, $^3J_{6\text{-}7}$=6.9 Hz, $^3J_{6\text{-}5\alpha}$=9.5 Hz, 1H, H_6), 2.40 (td, $^3J_{4\text{-}5\alpha}$=$^3J_{4\text{-}6}$=3.5 Hz, $^3J_{4\text{-}5\beta}$=7.1 Hz, 1H, H_4), 2.59 (dd, $^3J_{7\text{-}6}$=6.9 Hz, ^2J=14.7 Hz, 1H, H_7), 2.72 (dd, $^3J_{7\text{-}6}$=6.9 Hz, ^2J=14.7 Hz, 1H, H_7), 3.38-3.42 (m, 2H, H_3), 4.19-4.25 (m, 2H, H_2),

7.20-7.32 (m, 5H, H_{arom}); **^{13}C NMR** (*trans*, 125 MHz, $CDCl_3$): δ 13.0 (C_5), 20.3 (C_6), 32.1 (C_4), 37.8 (C_7), 45.7 (C_3), 61.8 (C_2), 126.2 (CH), 128.2 (CH), 128.3 (CH), 140.5 (C_q), 158.4 (C_1); **^{1}H NMR** (*cis*, 500 MHz, $CDCl_3$): δ 0.78 (dt, $^3J_{5\alpha\text{-}4}$=4.2 Hz, $^3J_{5\alpha\text{-}5\beta}$=$^3J_{5\alpha\text{-}6}$=6.3 Hz, 1H, $H_{5\alpha}$), 1.05-1.15 (m, 2H, $H_{5\beta}$ and H_6), 2.44 (dd, $^3J_{7\text{-}6}$=9.2 Hz, ^2J=15.7 Hz, 1H, H_7), 2.65 (ddd, $^3J_{4\text{-}5\alpha}$=4.2 Hz, ^3J=6.9 Hz, ^3J=7.7 Hz, 1H, H_4), 3.11 (dd, $^3J_{7\text{-}6}$=5.1 Hz, ^2J=15.0 Hz, 1H, H_7), 3.51-3.57 (m, 2H, H_3), 4.28-4.33 (m, 2H, H_2), 7.20-7.32 (m, 5H, H_{arom}); **^{13}C NMR** (*cis*, 100 MHz, $CDCl_3$): δ 11.1 (C_5), 18.7 (C_6), 31.0 (C_4), 33.7 (C_7), 46.9 (C_3), 62.0 (C_2), 126.0 (CH), 128.2 (CH), 141.0 (C_q), 159.7 (C_1); **CI(methane)-MS** *m/z* (%): 218 (MH^+, 17), 126 ([M-Bn]$^+$, 100), 115 (11), 104 (15), 91 (Bn^+, 22), 82 (12), 77 (Ph^+, 7), 65 (8), 54 (9) ; **HMRS**: MH^+, found 218.11777. $C_{13}H_{16}NO_2$ requires 218.11809.

(±)-1,2-diphenyl-2-aminoethanol 111



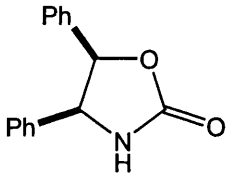
$C_{14}H_{15}NO$ 213.28 g.mol^{-1}

A mixture of α-benzoin oxime (25.0 g, 0.11 mol, 1 eq), Pd/C (5%, 2 g, 0.71 mmol, 0.0065 eq), absolute ethanol (325 mL) and hydrochloric acid (5-6M solution in isopropanol, 30 mL) was hydrogenated at 4 bar for 1 h. Water (200 mL) was added in order to dissolve the amine hydrochloride and the reaction mixture was then filtered. The filtrate was diluted to 800 mL with water and concentrated ammonia solution (100 mL) was added. The resulting precipitate was filtered, washed with water (3 x 50 mL), dried at 50°C *in vacuo* for 18 h to give the *title compound* **111** (22.1 g, 0.104 mol, 94%, *erythro/threo*: 93:7 as determined by ^{1}H NMR) as a white solid which was used without further purification.

IR (CH_2Cl_2): ν_{max} 3465 (w), 3380 (w), 3063 (m), 2963 (m), 2891 (w), 1593 (w), 1495 w), 1453 (m), 1277 (w), 1019 (m), 978 (w), 752 (s), 697 (s) cm^{-1}; **^{1}H NMR** (*erythro*, 300 MHz, $CDCl_3$): δ 4.16 (d, ^3J=6.3 Hz, 1H, C*H*NH_2), 4.75 (d, ^3J=6.3 Hz, 1H, C*H*OH), 7.15-7.7.35 (m, 10H, H_{arom}); **^{13}C NMR** (*erythro*, 75 MHz, $CDCl_3$): δ 61.9 ($CHNH_2$),

78.4 (CHOH), 127.0 (CH), 127.6 (CH), 127.7 (CH), 127.8 (CH), 128.3 (CH), 140.6 (C_q), 141.5 (C_q); **^{1}H NMR** (*threo*, 300 MHz, $CDCl_3$): δ 3.98 (d, ^3J=6.5 Hz, 1H, C*H*NH_2), 4.65 (d, ^3J=6.5 Hz, 1H, C*H*OH), 7.15-7.35 (m, 10H, H_{arom}).

(±)-*cis*-4,5-Diphenyl- 2-oxazolidinone (±)-112

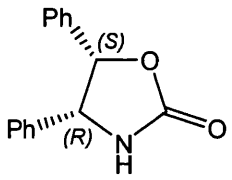


$C_{15}H_{13}NO_2$ 239.27 g.mol^{-1}

A solution of triphosgene (2.58 g, 8.68 mmol, 0.35 eq) in dry dichloromethane (10 mL) was added dropwise over 45 min to a suspension of amino alcohol **111** (5.3 g, 24.8 mmol, 1 eq) and triethylamine (7.6 mL, 54.56 mmol, 2.2 eq) in dry dichloromethane (70 mL) under nitrogen at 4°C. The reaction mixture was stirred for a further 15 min at 4 °C and then allowed to warm to room temperature and stirred for 1 h. Saturated aqueous NH_4Cl solution (25 mL) and dichloromethane (50 mL) were added to the reaction mixture and after stirring for 20 min, the mixture was transfered into a separating funnel. The aqueous layer was separated and the organic layer washed with water (25 mL). The combined aqueous layers were extracted with dichloromethane (50 mL) and the combined organic extracts were then dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude product was recrystallised twice from EtOAc-isohexane to give the *title compound* **112** (4.07 g, 17.0 mmol, 69%) as a white solid.

Mp 191-192°C (EtOAc/isohexane) (lit.,[134] 193.5-194.5°C (EtOAc/hexane)); R_f (isohexane/EtOAc 5.5/4.5) 0.3; **IR** ($CDCl_3$): ν_{max} 3278 (br, NH), 1752 (s, C=O), 1499 (w), 1446 (m), 1393 (w), 1350 (w), 1221 (w), 1071 (w), 1022 (w), 914 (w), 749 (m), 670 (s) cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 5.17 (d, ^3J=8.0 Hz, 1H, C*H*NH), 5.42 (br s, 1H, NH), 5.94 (d, ^3J=8.0 Hz, 1H, C*H*O), 6.90-6.98 (m, 4H, H_{arom}), 7.06-7.11 (m, 6H, H_{arom}); **^{13}C NMR** (75 MHz, $CDCl_3$): δ61.4 (CHNH), 82.3 (CHO), 126.9 (CH), 127.9 (CH), 128.1 (CH), 128.3 (CH), 134.4 (C_q), 136.0 (C_q), 159.6 (C=O).

(4*R*,5*S*)-(+)-4,5-Diphenyl- 2-oxazolidinone (+)-112



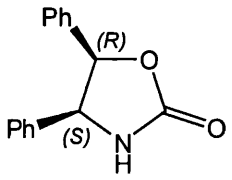
$C_{15}H_{13}NO_2$ 239.27 g.mol^{-1}

A solution of triphosgene (1.70 g, 5.74 mmol, 0.35 eq) in dry dichloromethane (8 mL) was added dropwise over 1.5 h to a suspension of (1*S*,2*R*)-2-amino-1,2-diphenylethanol (3.5 g, 16.41 mmol, 1 eq) and triethylamine (5.03 mL, 36.1 mmol, 2.2 eq) in dry dichloromethane (80 mL) under nitrogen at 4°C. The reaction mixture was stirred for 1.5 h at 4 °C, followed by a further addition of triphosgene (0.25 g, 0.84 mmol, 0.05 eq) and stirring for 30 min. Saturated aqueous NH_4Cl solution (25 mL) was added to the reaction mixture and after stirring for 5 min, the mixture was transfered into a separating funnel. The aqueous layer was separated and the organic layer washed with water (25 mL). The combined aqueous layers were extracted with EtOAc (50 mL) and the combined organic extracts were then dried ($MgSO_4$), filtered and concentrated *in vacuo* to give the *title compound* **(+)-112** contaminated by traces of triethylamine hydrochloride (3.21 g, 13.42 mmol, 82%) as a white solid.

R_f, IR, ^1H and ^{13}C NMR data were identical to the one given for the corresponding racemate **(±)-112**.

Mp 232-233°C (lit.,[13] 232.5-233.5°C (toluene)); $[\alpha]_D^{20}$ +66.3 (*c* 0.85, MeOH) (lit.,[13] $[\alpha]_D^{20}$ +60.6 (*c* 0.858, MeOH)).

(4*S*,5*R*)-(-)-4,5-Diphenyl- 2-oxazolidinone (-)-112



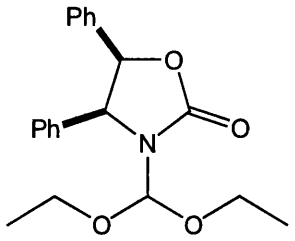
$C_{15}H_{13}NO_2$ 239.27 g.mol^{-1}

A solution of triphosgene (1.05 g, 3.53 mmol, 0.35 eq) in dry dichloromethane (5 mL) was added dropwise over 1 h to a suspension of (1*R*,2*S*)-2-amino-1,2-diphenylethanol (2.15 g, 10.08 mmol, 1 eq) and triethylamine (3.09 mL, 22.18 mmol, 2.2 eq) in dry dichloromethane (45 mL) under nitrogen at 4°C. The reaction mixture was stirred for a further 1 h at 4 °C and saturated aqueous NH_4Cl solution (25 mL) was added to the reaction mixture. The aqueous layer was extracted with dichloromethane (2 x 25 mL) and the combined organic extracts were then dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was partitioned between EtOAc (150 mL) and aqueous $NaHCO_3$ solution (5%, 50 mL). The organic layer was separated and then washed with brine (25 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to give the *title compound* **(-)-112** (2.05 g, 8.57 mmol, 85%) as a white solid.

R_f, IR, ^1H and ^{13}C NMR data were identical to the one given for the corresponding racemate **(±)-112**.

Mp 231-232°C; $[\alpha]_D^{20}$ -59.6 (*c* 0.86, MeOH) (lit.,[135] $[\alpha]_D^{27}$ -58.4 (*c* 0.91, MeOH)).

(±)-3-Diethoxymethyl-4,5-diphenyl-2-oxazolidinone (±)-113



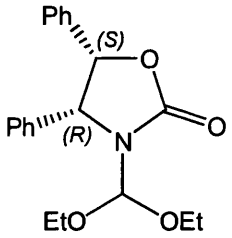
$C_{20}H_{23}NO_4$ 341.41 g.mol^{-1}

A mixture of 4,5-diphenyl-2-oxazolidinone **(±)-112** (5.0 g, 20.9 mmol, 1 eq), aluminium chloride (0.41 g, 3.1 mmol, 0.15 eq) and triethyl orthoformate (103 mL, 0.63 mol, 30 eq) was heated at 155°C for 24 h. The reaction mixture was cooled to room temperature and then quenched with saturated aqueous $NaHCO_3$ solution (50 mL). The aqueous phase was extracted with diethyl ether (200 mL then 100 mL) and the combined organic extracts were washed with brine (50 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (silica, isohexane/EtOAc 6.5:3.5) to give the *title compound* **(±)-113** (5.72 g, 16.75 mmol, 80%) as a white solid which can readily be recrystallised in hexane.

Mp 93.5-94.5°C (hexane); R_f (isohexane/EtOAc 5.5/4.5) 0.6; **IR** (film): ν_{max} 2979 (m), 1735 (s, C=O), 1455 (m), 1414 (m), 1385 (m), 1161 (m), 1102 (s), 1066 (s), 1037 (m), 1025 (m), 763 (m), 713 (m), 697 (m) cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 0.72 (t, ^3J=7.1 Hz, 3H, CH_2CH_3), 1.30 (t, ^3J=7.1 Hz, 3H, CH_2CH_3), 3.24 (qd, ^3J=7.1 Hz, ^2J=9.2 Hz, 1H, CH_2CH_3), 3.47 (qd, ^3J=7.1 Hz, ^2J=9.2 Hz, 1H, CH_2CH_3), 3.66 (qd, ^3J=7.1 Hz, ^2J=9.2 Hz, 1H, CH_2CH_3), 3.75 (qd, ^3J=7.1 Hz, ^2J=9.2 Hz, 1H, CH_2CH_3), 5.25 (d, ^3J=8.2 Hz, 1H, CHN), 5.87 (s, 1H, OCHO), 5.91 (d, ^3J=8.2 Hz, 1H, CHO), 6.93-7.12 (m, 10H, H_{arom}); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 14.0 (CH_3), 14.9 (CH_3), 60.5 (CHN), 62.6 (CH_2), 62.7 (CH_2), 81.5 (CHO), 102.0 (OCHO), 126.0 (CH), 127.6 (CH), 127.7 (2 x CH), 127.8 (CH), 134.2 (C_q), 136.4 (C_q), 157.4 (C=O); **^{1}H NMR** (400 MHz, DMSO): δ 0.65 (t, ^3J=7.1 Hz, 3H, CH_2CH_3), 1.19 (t, ^3J=7.1 Hz, 3H, CH_2CH_3), 3.20 (qd, ^3J=7.1 Hz, ^2J=9.3 Hz, 1H, CH_2CH_3), 3.41 (qd, ^3J=7.1 Hz, ^2J=9.3 Hz, 1H, CH_2CH_3), 3.58-3.66 (m, 2H, CH_2CH_3), 5.35 (d, ^3J=8.1 Hz, 1H, CHN), 5.77 (s, 1H, OCHO), 6.03 (d, ^3J=8.1 Hz, 1H, CHO), 6.90-7.12 (m, 10H, H_{arom}); **^{13}C**

NMR (100 MHz, DMSO): δ 14.0 (CH_3), 14.8 (CH_3), 59.4 (CHN), 61.6 (CH_2), 61.9 (CH_2), 80.3 (CHO), 101.6 (OCHO), 126.0 (CH), 127.2 (CH), 127.3 (CH), 127.5 (2 x CH), 127.6 (CH), 134.7 (C_q), 136.9 (C_q), 156.5 (C=O); **FAB-MS** *m/z* (%): 364 (MNa^+, 100), 296 ($[M\text{-}EtO]^+$, 14), 262 (46), 180 (5); **HMRS**: MNa^+, found 364.15313 $C_{20}H_{23}NNaO_4$ requires 364.15247; **Anal.** found: C, 70.32; H, 6.80; N, 4.10. Calcd for $C_{20}H_{23}NO_4$: C, 70.36; H, 6.79; N, 4.10.

(4*R*,5*S*)-(+)-3-Diethoxymethyl-4,5-diphenyl-2-oxazolidinone (+)-113



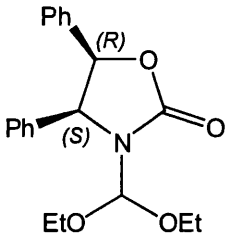
$C_{20}H_{23}NO_4$ 341.41 g.mol^{-1}

A mixture of (4*R*,5*S*)-(+)-4,5-diphenyl-2-oxazolidinone **(+)-112** (2.19 g, 9.15 mmol, 1 eq), aluminium chloride (0.18 g, 1.37 mmol, 0.15 eq) and triethyl orthoformate (45 mL, 0.27 mol, 30 eq) was heated at 155°C for 44 h. The reaction mixture was cooled to room temperature and then quenched with saturated aqueous $NaHCO_3$ solution (25 mL). The aqueous phase was extracted with diethyl ether (90 mL then 45 mL) and the combined organic extracts were washed with brine (25 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (silica, P.E. 30-40°C/EtOAc 8.5:1.5 to 3:1) to give the *title compound* **(+)-113** (2.29 g, 6.71 mmol, 74%) as a white solid which can readily be recrystallised in hexane.

R_f, IR, ^{1}H and ^{13}C NMR, and mass spectra data were identical to the one given for the corresponding racemate **(±)-113**.

Mp 93-95°C (hexane); $[\alpha]_D^{20}$ +6.0 (*c* 0.55, CH_2Cl_2); **Anal.** found: C, 70.19; H, 6.79; N, 4.15. Calcd for $C_{20}H_{23}NO_4$: C, 70.36; H, 6.79; N, 4.10.

(4*S*,5*R*)-(-)-3-Diethoxymethyl-4,5-diphenyl-2-oxazolidinone (-)-113



$C_{20}H_{23}NO_4$ 341.41 g.mol^{-1}

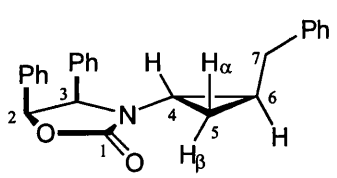
A mixture of (4*S*,5*R*)-(-)-4,5-diphenyl-2-oxazolidinone **(-)-112** (0.8 g, 3.34 mmol, 1 eq), aluminium chloride (67 mg, 0.5 mmol, 0.15 eq) and triethyl orthoformate (16.5 mL, 0.1 mol, 30 eq) was heated at 160°C for 20 h. The reaction mixture was cooled to room temperature and then quenched with saturated aqueous $NaHCO_3$ solution (10 mL). The aqueous phase was extracted with EtOAc (30 mL then 2 x 15 mL) and the combined organic extracts were washed with brine (10 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (silica, P.E. 30-40°C/EtOAc 8.5:1.5 to 3:1) to give the *title compound* **(-)-113** (0.78 g, 2.28 mmol, 68%) as a white solid which can readily be recrystallised in hexane.

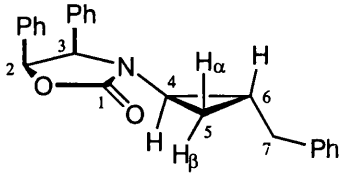
R_f, IR, ^{1}H and ^{13}C NMR, and mass spectra data were identical to the one given for the corresponding racemate **(±)-113**.

Mp 92.5-94.5°C (hexane); $[\alpha]_D^{26}$ -4.5 (*c* 1.12, CH_2Cl_2); **Anal.** found: C, 70.32; H, 6.75; N, 4.12. Calcd for $C_{20}H_{23}NO_4$: C, 70.36; H, 6.79; N, 4.10.

(±)-3-(2-Benzylcyclopropyl)-4,5-diphenyl-2-oxazolidinone (±)-114

trans isomer A





trans isomer B

$C_{25}H_{23}NO_2$ 369.47 g.mol^{-1}

A solution of 3-diethoxymethyl-4,5-diphenyl-2-oxazolidinone **(±)-113** (0.80 g, 2.34 mmol, 1.5 eq) in dry drichloromethane (2.5 mL) was added *via* a motorised syringe pump over 6 h to a vigorously stirred mixture of zinc amalgam (1.53 g, 23.4 mmol, 15 eq), zinc chloride (1M solution in diethyl ether, 2.34 mL, 2.34 mmol, 1.5 eq), chlorotrimethylsilane (1.48 mL, 11.7 mmol, 7.5 eq) and allylbenzene (0.184 g, 1.56 mmol, 1 eq) in dry diethyl ether (7.5 mL) under nitrogen at reflux. The mixture was stirred for 16 h and then allowed to cool to room temperature. Dichloromethane (10 mL) was added and the reaction was quenched with saturated aqueous $NaHCO_3$ solution (20 mL) and after stirring for 20 min, the mixture was filtered through celite and the separated zinc washed with dichloromethane (20 mL). The organic solvents were removed *in vacuo* and the aqueous layer was extracted with dichloromethane (3 x 20 mL). The combined organic extracts were washed with brine (20 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (silica, isohexane/EtOAc 3:1 to 7:3) to give a mixture of cyclopropanes **(±)-114** contaminated by 10 wt. % of 4,5-diphenyl-*N*-formyl-2-oxazolidinone (531 mg, 1.29 mmol of **(±)-114** after correction, 83% of **(±)-114** after correction; **(±)-114A:(±)-114B:(±)-114C:(±)-114D**: 84:12:<2:<2 as determined by ^{1}H NMR) as a white solid.

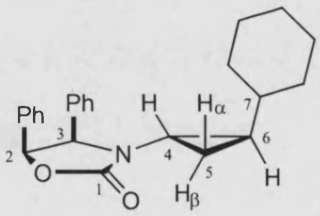
Isomer A: R_f (P.E. 40-60°C/EtOAc 3:1) 0.33; **IR** ($CDCl_3$): ν_{max} 3064 (w), 3031 (w), 2920 (w), 1756 (s, C=O), 1606 (w, C=C), 1497 (w), 1451 (w), 1405 (m), 1217 (w), 1194 (w), 1137 (w), 1079 (w), 1026 (w), 762 (w), 722 (w), 697 (s) cm^{-1}; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 0.93 (dt, $^2J_{5\alpha\text{-}5\beta}$=$^3J_{5\alpha\text{-}6}$=5.9 Hz, $^3J_{5\alpha\text{-}4}$=7.0 Hz, 1H, $H_{5\alpha}$), 1.24 (m, 1H, H_6), 1.31 (ddd, $^3J_{5\beta\text{-}4}$=3.7 Hz, $^2J_{5\beta\text{-}5\alpha}$=5.7 Hz, $^3J_{5\beta\text{-}6}$=9.4 Hz, 1H, $H_{5\beta}$), 2.18 (dd, $^3J_{7\text{-}6}$=7.7 Hz, ^2J=14.5 Hz, 1H, H_7), 2.31 (dt, $^3J_{4\text{-}5\beta}$=$^3J_{4\text{-}6}$=3.5 Hz, $^3J_{4\text{-}5\alpha}$=7.0 Hz, 1H, H_4), 2.57 (dd, $^3J_{7\text{-}6}$=5.6 Hz, ^2J=14.5 Hz, 1H, H_7), 4.68 (d, $^3J_{3\text{-}2}$=7.9 Hz, 1H, H_3), 5.69 (d, $^3J_{2\text{-}3}$=7.9

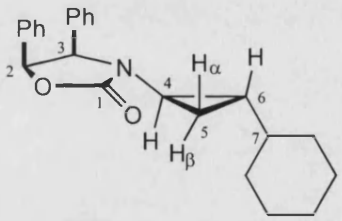
Hz, 1H, H_2), 6.72-6.78 (m, 2H, H_{arom}), 6.86-6.97 (m, 4H, H_{arom}), 7.03-7.14 (m, 9H, H_{arom}); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 14.2 (C_5), 20.9 (C_6), 31.2 (C_4), 37.7 (C_7), 66.8 (C_3), 79.7 (C_2), 126.0 (CH), 126.1 (CH), 127.6 (CH), 127.8 (CH), 128.1 (CH), 128.2 (CH), 128.3 (CH), 128.4 (CH), 134.3 (2 x C_q), 140.3 (C_q), 158.0 (C_1); **CI(methane)-MS** *m/z* (%): 370 (MH^+, 100), 354 (8), 326 ($[M+H-CO_2]^+$, 52), 292 ($[M-Ph]^+$, 13), 278 ($[M-Bn]^+$, 17), 248 (12), 234 (19), 208 (7), 197 (12), 180 (37), 131 (17), 117 (11), 91 (Bn^+, 19), 77 (Ph^+, 4); **HMRS**: MH^+, found 370.18044. $C_{25}H_{24}NO_2$ requires 370.18069.

Isomer B: R_f (P.E. 40-60°C/EtOAc 3:1) 0.27; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 0.53 (dt, $^2J_{5\beta\text{-}5\alpha}$=$^3J_{5\beta\text{-}6}$=6.2 Hz, $^3J_{5\beta\text{-}4}$=7.1 Hz, 1H, $H_{5\beta}$), 0.85 (ddd, $^3J_{5\alpha\text{-}4}$=3.7 Hz, $^2J_{5\alpha\text{-}5\beta}$=5.6 Hz, $^3J_{5\alpha\text{-}6}$=9.4 Hz, 1H, $H_{5\alpha}$), 1.61 (ddddd, $^3J_{6\text{-}4}$=3.1 Hz, $^3J_{6\text{-}7}$=5.6 Hz, $^3J_{6\text{-}5\beta}$=6.2 Hz, $^3J_{6\text{-}7}$=8.6 Hz, $^3J_{6\text{-}5\alpha}$=9.3 Hz, 1H, H_6), 2.29 (dd, $^3J_{7\text{-}6}$=8.6 Hz, ^2J=14.8 Hz, 1H, H_7), 2.35 (dt, $^3J_{4\text{-}5\alpha}$=$^3J_{4\text{-}6}$=3.4 Hz, $^3J_{4\text{-}5\beta}$=7.0 Hz, 1H, H_4), 3.05 (dd, $^3J_{7\text{-}6}$=5.4 Hz, ^2J=14.8 Hz, 1H, H_7), 4.80 (d, $^3J_{3\text{-}2}$=7.9 Hz, 1H, H_3), 5.74 (d, $^3J_{2\text{-}3}$=7.9 Hz, 1H, H_2), 6.70-7.15 (m, 15H, H_{arom}); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 12.3 (C_5), 21.5 (C_6), 31.5 (C_4), 37.9 (C_7), 66.5 (C_3), 79.7 (C_2), 126.0 (CH), 127.6 (CH), 127.9 (CH), 128.3 (CH), 128.5 (CH), 134.7 (2 x C_q), 140.3 (C_q), 158.3 (C_1).

(±)-3-(2-Cyclohexylcyclopropyl)-4,5-diphenyl-2-oxazolidinone (±)-117

trans isomer A





trans isomer B

$C_{24}H_{27}NO_2$ 361.48 g.mol^{-1}

A solution of 3-diethoxymethyl-4,5-diphenyl-2-oxazolidinone **(±)-113** (0.47 g, 1.375 mmol, 1.25 eq) in dry drichloromethane (1.5 mL) was added *via* a motorised syringe pump over 6 h to a vigorously stirred mixture of zinc amalgam (0.90 g, 13.75 mmol, 12.5 eq), zinc chloride (1M solution in diethyl ether, 1.38 mL, 1.38 mmol, 1.25 eq), chlorotrimethylsilane (0.87 mL, 6.875 mmol, 6.25 eq) and vinylcyclohexane (0.121 g, 1.1 mmol, 1 eq) in dry diethyl ether (6 mL) under nitrogen at reflux. The mixture was

stirred for 16 h and then allowed to cool to room temperature. Dichloromethane (2 mL) was added and the reaction was quenched with saturated aqueous $NaHCO_3$ solution (15 mL) and after stirring for 20 min, the mixture was filtered through celite and the separated zinc washed with dichloromethane (20 mL). The organic solvents were removed *in vacuo* and the aqueous layer was extracted with dichloromethane (3 x 15 mL). The combined organic extracts were washed with brine (15 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude product (**(±)-117A:(±)-117B:(±)-117C:(±)-117D**: 88:8:<2:<2 as determined by ^{1}H NMR) was purified by flash column chromatography (silica, isohexane/EtOAc 9:1 to 4:1) to give the cyclopropanes **(±)-117** (mixture of **(±)-117A**, **(±)-117B**, **(±)-117C**, **(±)-117D** 33 mg, 0.09 mmol, 8%, white solid; **(±)-117A** 263 mg, 0.73 mmol, 66%, white solid; 0.82 mmol, 74%).

Isomer A: **Mp** 146-148°C; R_f (P.E. 40-60°C/EtOAc 8.5:1.5) 0.26; **IR** ($CDCl_3$): ν_{max} 2924 (s), 2851 (m), 1751 (s, C=O), 1456 (m), 1406 (s), 1265 (s), 1196 (m), 1078 (m), 1026 (m), 741 (s), 698 (s) cm^{-1}; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 0.28-0.37 (m, 1H, H_7), 0.67-0.73 (m, 1H), 0.73-0.81 (m, 2H, H_6 and H_5), 0.88-0.97 (m, 2H), 0.99-1.15 (m, 4H), 1.39-1.52 (m, 2H), 1.55-1.66 (m, 2H), 2.17 (td, $^3J_{4\text{-}5\beta}$=$^3J_{4\text{-}6}$=3.5 Hz, $^3J_{4\text{-}5\alpha}$=6.7 Hz, 1H, H_4), 4.82 (d, $^3J_{3\text{-}2}$=8.0 Hz, 1H, H_3), 5.73 (d, $^3J_{2\text{-}3}$=8.0 Hz, 1H, H_2), 6.86-6.90 (m, 2H, H_{arom}), 6.95-6.99 (m, 2H, H_{arom}), 7.01-7.11 (m, 6H, H_{arom}); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 13.6 (C_5), 25.7 (CH_2), 25.8 (C_6 and CH_2), 26.2 (CH_2), 30.2 (C_4), 32.1 (2 x CH_2), 40.4 (C_7), 66.8 (C_3), 79.6 (C_2), 125.9 (CH), 127.6 (CH), 127.7 (2 x CH), 128.1 (CH), 128.2 (CH), 134.3 (C_q), 134.5 (C_q), 158.2 (C_1); **EI-MS** *m/z* (%): 361 (M^+, 3), 278 (11), 234 (43), 180 (100), 165 (7), 132 (5), 104 (9), 77 (Ph^+, 5); **HMRS**: M^+, found 361.20933. $C_{24}H_{27}NO_2$ requires 361.20417. **Anal.** found: C, 79.56; H, 7.82; N, 3.74. Calcd for $C_{24}H_{27}NO_2$: C, 79.74; H, 7.53; N, 3.87.

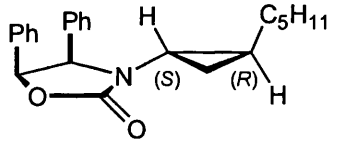
Isomer B: R_f (P.E. 40-60°C/EtOAc 8.5:1.5) 0.35; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 0.36 (ddd, $^2J_{5\beta\text{-}5\alpha}$=5.5 Hz, $^3J_{5\beta\text{-}6}$=6.4 Hz, $^3J_{5\beta\text{-}4}$=7.3 Hz, 1H, $H_{5\beta}$), 0.53-0.62 (m, 1H, H_6), 0.67 (ddd, $^3J_{5\alpha\text{-}4}$=3.7 Hz, $^2J_{5\alpha\text{-}5\beta}$=5.4 Hz, $^3J_{5\alpha\text{-}6}$=9.2 Hz, 1H, $H_{5\alpha}$), 0.94-1.33 (m, 6H), 1.54-1.76 (m, 4H), 1.94-2.02 (m, 1H), 2.18 (dt, $^3J_{4\text{-}5\alpha}$=$^3J_{4\text{-}6}$=3.5 Hz, $^3J_{4\text{-}5\beta}$=7.1 Hz, 1H, H_4), 4.80 (d, $^3J_{3\text{-}2}$=7.9 Hz, 1H, H_2), 5.70 (d, $^3J_{2\text{-}3}$=7.9 Hz, 1H, H_2), 6.85-7.14 (m, 10H, H_{arom}); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 10.9 (C_5), 26.1 (2 x CH_2), 26.4 (CH_2), 27.3 (C_6), 30.5 (C_4), 32.0 (CH_2), 32.4 (CH_2), 41.0 (C_7), 66.6 (C_3), 79.5 (C_2), 126.0 (CH), 127.7 (CH), 127.8 (CH), 128.2 (CH), 128.4 (CH), 134.5 (C_q), 134.8 (C_q), 158.2 (C_1).

General procedure for the cyclopropanation of vinyl cyclohexane using chiral 3-diethoxymethyl-4,5-diphenyl-2-oxazolidinone (+)-113 or (-)-113

A solution of chiral 3-diethoxymethyl-4,5-diphenyl-2-oxazolidinone **(+)-113** or **(-)-113** (1.25 mmol, 1.25 eq) in dry drichloromethane (1.5 mL) was added *via* a motorised syringe pump over 6 h to a vigorously stirred mixture of zinc amalgam (0.82 g, 12.5 mmol, 12.5 eq), zinc chloride (1M solution in diethyl ether, 1.25 mL, 1.25 mmol, 1.25 eq), chlorotrimethylsilane (0.79 mL, 6.25 mmol, 6.25 eq) and vinyl cyclohexane (0.11 g, 1.0 mmol, 1 eq) in dry diethyl ether (5.5 mL) under nitrogen at reflux. The mixture was stirred for 16 h and then allowed to cool to room temperature. The reaction mixture was quenched with saturated aqueous $NaHCO_3$ solution (10 mL) and after stirring for 20 min, the mixture was filtered and the separated zinc washed with dichloromethane (10 mL). The organic solvents were removed *in vacuo* and the aqueous layer was extracted with dichloromethane (3 x 10 mL). The combined organic extracts were washed with brine (10 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*.

R_f, IR, ^1H and ^{13}C NMR, and mass spectra data of these products were identical to the one given for the corresponding racemate **(±)-117**.

(4*R*,5*S*)-3-((1*S*,2*R*)-2-Cyclohexylcyclopropyl)-4,5-diphenyl-2-oxazolidinone (+)-117

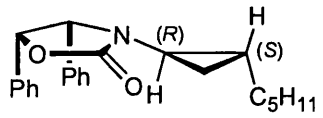


$C_{24}H_{27}NO_2$ 361.48 g.mol^{-1}

Following the general procedure, the crude product (**(+)-117A:(+)-117B:(+)-117C:(+)-117D**: 88:8:<2:<2 as determined by ^1H NMR), obtained by the reaction between vinyl cyclohexane and **(+)-113**, was purified by flash column chromatography (silica, P.E. 40-60°C/EtOAc 9:1 to 4:1) to give the cyclopropanes **(+)-117** (mixture of **(+)-117A**, **(+)-117B**, **(+)-117C**, **(+)-117D** 26 mg, 0.072 mmol, 7%, white solid; **(+)-117A** 179 mg, 0.50 mmol, 50%, white solid; 0.57 mmol, 57%).

Isomer A: **Mp** 136.5-138.5°C (EtOAc/hexane); $[\alpha]_D^{18}$ +98.7 (*c* 1.07, $CHCl_3$); **Anal.** found: C, 79.64; H, 7.56; N, 3.87. Calcd for $C_{24}H_{27}NO_2$: C, 79.74; H, 7.53; N, 3.87.

(4*S*,5*R*)-3-((1*R*,2*S*)-2-Cyclohexylcyclopropyl)-4,5-diphenyl-2-oxazolidinone (-)-117



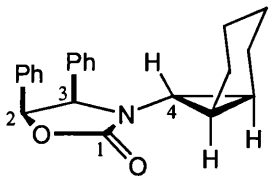
$C_{24}H_{27}NO_2$ 361.48 g.mol^{-1}

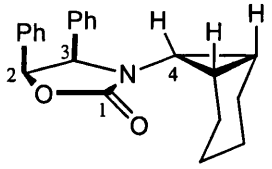
Following the general procedure, the crude product (**(-)-117A:(-)-117B:(-)-117C:(-)-117D**: 88:8:<2:<2 as determined by ^{1}H NMR), obtained by the reaction between vinyl cyclohexane (110 mg, 1.0 mmol) in dry diethyl ether (5.25 mL) and a solution of **(-)-113** in dry dichloromethane (1.5 mL) added over 6 h, was purified by flash column chromatography (silica, P.E. 40-60°C/EtOAc 9:1 to 4:1) to give the cyclopropanes **(-)-117** (mixture of **(-)-117A**, **(-)-117B**, **(-)-117C**, **(-)-117D** 33 mg, 0.09 mmol, 8%, white solid; **(-)-117A** 263 mg, 0.73 mmol, 66%, white solid; 0.82 mmol, 74%).

Isomer A: **Mp** 136-139°C (EtOAc/hexane); $[\alpha]_D^{23}$ -106.9 (*c* 1.07, $CHCl_3$).

(±)-3-Bicyclo[4.1.0]hept-7-yl-4,5-diphenyl-2-oxazolidinone (±)-118

exo
isomer A





endo
isomer C

$C_{22}H_{23}NO_2$ 333.43 g.mol^{-1}

A solution of 3-diethoxymethyl-4,5-diphenyl-2-oxazolidinone **(±)-113** (0.64 g, 1.88 mmol, 1.25 eq) in dry drichloromethane (2.5 mL) was added *via* a motorised syringe pump over 6.5 h to a vigorously stirred mixture of zinc amalgam (1.23 g, 18.8 mmol, 12.5 eq), zinc chloride (1M solution in diethyl ether, 1.88 mL, 1.88 mmol, 1.25 eq),

chlorotrimethylsilane (1.19 mL, 9.38 mmol, 6.25 eq) and cyclohexene (0.123 g, 1.50 mmol, 1 eq) in dry diethyl ether (7.6 mL) under nitrogen at reflux. The mixture was stirred for 14 h and then allowed to cool to room temperature. Dichloromethane (2 mL) was added and the reaction was quenched with saturated aqueous $NaHCO_3$ solution (20 mL) and after stirring for 20 min, the mixture was filtered through celite and the separated zinc washed with dichloromethane (20 mL). The organic solvents were removed *in vacuo* and the aqueous layer was extracted with dichloromethane (3 x 20 mL). The combined organic extracts were washed with brine (20 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude product (**(±)-118A:(±)-118B:(±)-118C:(±)-118D**: 90:<2:6:<2 as determined by ^{1}H NMR) was purified by flash column chromatography (silica, isohexane/EtOAc 4:1 to 3:1) to give the cyclopropanes **(±)-118** (mixture of **(±)-118A**, **(±)-118B**, **(±)-118C**, **(±)-118D** 19 mg, 0.06 mmol, 4%, white solid; **(±)-118A** 0.271 mg, 0.81 mmol, 54%, white solid; 0.87 mmol, 58%).

Isomer A: **Mp** 154-156°C; R_f (isohexane/EtOAc 3:1) 0.34; **IR** ($CDCl_3$): ν_{max} 3035 (w), 2929 (m), 2855 (w), 1755 (s, C=O), 1499 (w), 1455 (m), 1404 (m), 1218 (w), 1197 (w), 1121 (w), 1080 (w), 1026 (w), 763 (m), 702 (m) cm^{-1}; **^{1}H NMR** (500 MHz, $CDCl_3$): δ0.86-1.06 (m, 2H), 1.07-1.24 (m, 4H), 1.48 (dddd, ^3J=2.2 Hz, ^3J=3.4 Hz, ^3J=7.1 Hz, ^3J=10.0 Hz, 1H), 1.68-1.95 (m, 3H), 2.10 (t, ^3J=3.4 Hz, 1H, H_4), 4.86 (d, $^3J_{3\text{-}2}$=8.0 Hz, 1H, H_3), 5.75 (d, $^3J_{2\text{-}3}$=8.0 Hz, 1H, H_2), 6.89-6.93 (m, 2H, H_{arom}), 6.97-7.01 (m, 2H, H_{arom}), 7.05-7.14 (m, 6H, H_{arom}); **^{13}C NMR** (125 MHz, $CDCl_3$): δ17.5 (CH), 20.0 (CH), 21.0 (CH_2), 21.1 (CH_2), 22.0 (CH_2), 22.2 (CH_2), 36.1 (C_4), 66.3 (C_3), 79.5 (C_2), 125.9 (CH), 127.7 (2 x CH), 127.8 (CH), 128.1 (CH), 128.2 (CH), 134.6 (2 x C_q), 158.1 (C_1); **CI(methane)-MS** *m/z* (%): 334 (MH^+, 100), 290 ($[M+H-CO_2]^+$, 100), 256 ($[M-Ph]^+$, 16), 208 (12), 130 (11), 91 (6); **HMRS**: MH^+, found 334.18079. $C_{22}H_{24}NO_2$ requires 334.18069. **Anal.** found: C, 79.13; H, 6.98; N, 4.24. Calcd for $C_{22}H_{23}NO_2$: C, 79.25; H, 6.95; N, 4.20.

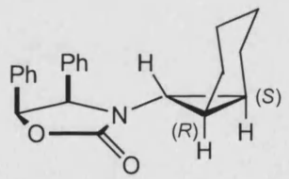
Isomer C: R_f (isohexane/EtOAc 3:1) 0.43; **^{1}H NMR** (500 MHz, $CDCl_3$): δ0.85 (dddd, ^3J=2.1 Hz, ^3J=7.3 Hz, ^3J=9.5 Hz, ^3J=11.6 Hz, 1H), 1.15-2.11 (m, 9H), 2.30 (t, ^3J=7.4 Hz, 1H, H_4), 4.98 (d, $^3J_{3\text{-}2}$=7.4 Hz, 1H, H_3), 5.84 (d, $^3J_{2\text{-}3}$=7.4 Hz, 1H, H_2), 6.89-7.16 (m, 10H, H_{arom}); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 12.3 (CH), 13.7 (CH), 18.7 (CH_2), 20.3 (CH_2), 22.3 (2 x CH_2), 32.3 (C_4), 67.0 (C_3), 79.9 (C_2), 126.0 (CH), 127.8 (CH), 127.9 (CH), 128.3 (CH), 128.4 (CH), 134.1 (2 x C_q), 159.6 (C_1).

General procedure for the cyclopropanation of cyclohexene using chiral 3-diethoxymethyl-4,5-diphenyl-2-oxazolidinone (+)-113 or (-)-113

A solution of chiral 3-diethoxymethyl-4,5-diphenyl-2-oxazolidinone **(+)-113** or **(-)-113** (1.25 mmol, 1.25 eq) in dry drichloromethane (1.5 mL) was added *via* a motorised syringe pump over 6 h to a vigorously stirred mixture of zinc amalgam (0.82 g, 12.5 mmol, 12.5 eq), zinc chloride (1M solution in diethyl ether, 1.25 mL, 1.25 mmol, 1.25 eq), chlorotrimethylsilane (0.79 mL, 6.25 mmol, 6.25 eq) and cyclohexene (82 mg, 1.0 mmol, 1 eq) in dry diethyl ether (5.5 mL) under nitrogen at reflux. The mixture was stirred for 16 h and then allowed to cool to room temperature. The reaction mixture was quenched with saturated aqueous $NaHCO_3$ solution (10 mL) and after stirring for 20 min, the mixture was filtered and the separated zinc washed with dichloromethane (10 mL). The organic solvents were removed *in vacuo* and the aqueous layer was extracted with dichloromethane (3 x 10 mL). The combined organic extracts were washed with brine (10 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*.

R_f, IR, ^1H and ^{13}C NMR, and mass spectra data of these products were identical to the one given for the corresponding racemate **(±)-118**.

(4*R*,5*S*)-3-((1*R*,6*S*)-Bicyclo[4.1.0]hept-7-yl)-4,5-diphenyl-2-oxazolidinone (+)-118

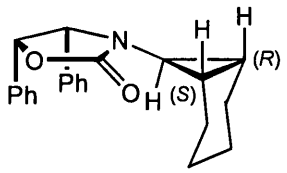


$C_{22}H_{23}NO_2$ 333.43 g.mol^{-1}

Following the general procedure, the crude product (**(+)-118A:(+)-118B:(+)-118C:(+)-118D**: 90:<2:6:<2 as determined by ^1H NMR), obtained by the reaction between cyclohexene (82 mg, 1.0 mmol) in dry diethyl ether (5.25 mL) and a solution of **(+)-113** in dry dichloromethane (1.5 mL) added over 6 h, was purified by flash column chromatography (silica, P.E. 40-60°C/EtOAc 4:1 to 3:1) to give the cyclopropanes **(+)-118** (mixture of **(+)-118A**, **(+)-118B**, **(+)-118C**, **(+)-118D** 27 mg, 0.08 mmol, 4%, white solid; **(+)-118A** 0.175 mg, 0.53 mmol, 53%, white solid; 0.61 mmol, 61%).

Isomer A: **Mp** 176-179°C (EtOAc); $[\alpha]_D^{19}$ +90.2 (*c* 1.05, $CHCl_3$); **Anal.** found: C, 79.32; H, 7.00; N, 4.20. Calcd for $C_{22}H_{23}NO_2$: C, 79.25; H, 6.95; N, 4.20.

(4*S*,5*R*)-3-((1*S*,6*R*)-Bicyclo[4.1.0]hept-7-yl)-4,5-diphenyl-2-oxazolidinone (-)-118



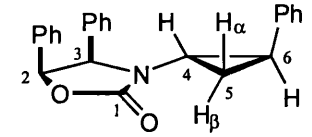
$C_{22}H_{23}NO_2$ 333.43 g.mol^{-1}

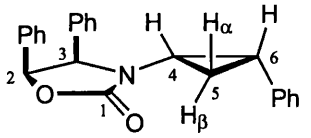
Following the general procedure, the crude product (**(-)-118A:(-)-118B:(-)-118C:(-)-118D**: 90:<2:6:<2 as determined by ^{1}H NMR), obtained by the reaction between cyclohexene (82 mg, 1.0 mmol) in dry diethyl ether (5.25 mL) and a solution of **(-)-113** in dry dichloromethane (1.5 mL) added over 6 h, was purified by flash column chromatography (silica, P.E. 40-60°C/EtOAc 4:1) to give the cyclopropanes **(-)-118** (mixture of **(-)-118A**, **(-)-118B**, **(-)-118C**, **(-)-118D** 22 mg, 0.066 mmol, 7%, white solid; **(-)-118A** 0.171 mg, 0.51 mmol, 51%, white solid; 0.58 mmol, 58%).

Isomer A: **Mp** 174-177°C (EtOAc); $[\alpha]_D^{22}$ -86.0 (*c* 0.86, $CHCl_3$).

(±)-3-(2-Phenylcyclopropyl)-4,5-diphenyl2-oxazolidinone (±)-119

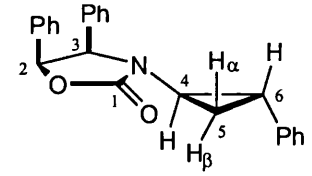
trans isomer A

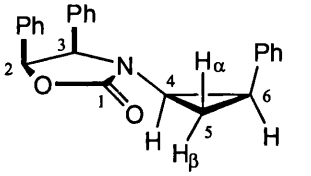




cis isomer C

trans isomer B





cis isomer D

$C_{24}H_{21}NO_2$ 355.43 g.mol^{-1}

A solution of 3-diethoxymethyl-4,5-diphenyl-2-oxazolidinone **(±)-113** (0.615 g, 1.8 mmol, 1.25 eq) in dry drichloromethane (2.5 mL) was added *via* a motorised syringe pump over 2 h to a vigorously stirred mixture of zinc amalgam (1.18 g, 18.0 mmol, 12.5 eq), zinc chloride (1M solution in diethyl ether, 1.8mL, 1.8 mmol, 1.25 eq), chlorotrimethylsilane (1.14 mL, 9.0 mmol, 6.25 eq) and styrene (0.15 g, 1.44 mmol, 1 eq) in dry diethyl ether (6.2 mL) under nitrogen at reflux. The mixture was stirred for 17 h and then allowed to cool to room temperature. Dichloromethane (2 mL) was added and the reaction was quenched with saturated aqueous $NaHCO_3$ solution (20 mL) and after stirring for 20 min, the mixture was filtered through celite and the separated zinc washed with dichloromethane (20 mL). The organic solvents were removed *in vacuo* and the aqueous layer was extracted with dichloromethane (3 x 20 mL). The combined organic extracts were washed with brine (20 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude product (**(±)-119A:(±)-119B:(±)-119C:(±)-119D**: 56:6:28:6 as determined by ^{1}H NMR) was purified by flash column chromatography (silica, isohexane/diethyl ether 3:2 to 1:1) to give a mixture of cyclopropanes **(±)-119** contaminated by traces of 4,5-diphenyl-*N*-formyl-2-oxazolidinone (mixture of **(±)-119A**, **(±)-119B**, **(±)-119C**, **(±)-119D** 0.121 g, 0.34 mmol, 24%, white solid; **(±)-119A** 0.161 g, 0.45 mmol, 31%, white solid; 0.79 mmol, 55%).

Isomer A: **Mp** 153-154°C (EtOAc/P.E. 40-60°C); R_f (isohexane/diethyl ether 1:1) 0.22; **IR** ($CDCl_3$): ν_{max} 3035 (w), 3000 (w), 2920 (w), 1738 (s, C=O), 1604 (w, C=C), 1499 (w), 1455 (m), 1403 (s), 1227 (m), 1194 (m), 1137 (w), 1134 (m); 1025 (s), 762 (s), 721 (s), 696 (s) cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$): δ 1.37 (td, $^2J_{5\alpha\text{-}5\beta}=^3J_{5\alpha\text{-}6}$=6.6 Hz,

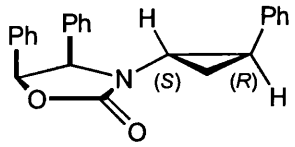
$^3J_{5\alpha\text{-}4}$=7.4 Hz, 1H, $H_{5\alpha}$), 1.37 (ddd, $^3J_{5\beta\text{-}4}$=4.2 Hz, $^2J_{5\beta\text{-}5\alpha}$=6.1 Hz, $^3J_{5\beta\text{-}6}$=10.1 Hz, 1H, $H_{5\beta}$), 2.22 (ddd, $^3J_{6\text{-}4}$=3.3 Hz, $^3J_{6\text{-}5\alpha}$=6.5 Hz, $^3J_{6\text{-}5\beta}$=9.8 Hz, 1H, H_6), 2.63 (td, $^3J_{4\text{-}5\beta}$=$^3J_{4\text{-}6}$=3.9 Hz, $^3J_{4\text{-}5\alpha}$=7.4 Hz, 1H, H_4), 5.04 (d, $^3J_{3\text{-}2}$=8.0 Hz, 1H, H_3), 5.83 (d, $^3J_{2\text{-}3}$=8.0 Hz, 1H, H_2), 6.80-7.15 (m, 15H, H_{arom}); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 15.9 (C_5), 23.4 (C_6), 33.9 (C_4), 66.7 (C_3), 79.7 (C_2), 126.0 (CH), 126.3 (CH), 126.8 (CH), 127.6 (CH), 127.9 (CH), 128.1 (CH), 128.2 (CH), 128.4 (CH), 134.3 (C_q), 134.4 (C_q), 139.4 (C_q), 157.9 (C_1); **EI-MS** *m/z* (%): 356 (MH^+, 2), 240 (79), 220 (24), 180 (100), 117 (90), 91 (68), 77 (Ph^+, 52); **HMRS**: MH^+, found 356.16306. $C_{24}H_{22}NO_2$ requires 356.16505.

Isomer B: R_f (isohexane/diethyl ether 1:1) 0.37; **^{1}H NMR** (300 MHz, $CDCl_3$): δ 1.05-1.29 (m, 2H, H_5), 2.40-2.57 (m, 2H, H_4 and H_6), 4.94 (d, $^3J_{3\text{-}2}$=7.9 Hz, 1H, H_3), 5.81 (d, $^3J_{2\text{-}3}$=7.9 Hz, 1H, H_2), 6.72-7.44 (m, 15H, H_{arom}); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 13.5 (C_5), 24.9 (C_6), 34.4 (C_4), 66.4 (C_3), 79.7 (C_2), 126.3 (CH), 127.0 (CH), 127.4 (CH), 127.8 (CH), 127.9 (CH), 128.3 (CH), 129.0 (CH), 134.4 (C_q), 134.6 (C_q), 139.4 (C_q), 158.6 (C_1);

Isomer C: R_f (isohexane/diethyl ether 1:1) 0.37; **^{1}H NMR** (300 MHz, $CDCl_3$): δ 1.53 (td, $^3J_{5\alpha\text{-}4}$=$^2J_{5\alpha\text{-}5\beta}$=7.3 Hz, $^3J_{5\alpha\text{-}6}$=9.0 Hz, 1H, $H_{5\alpha}$), 1.96 (dt, $^3J_{5\beta\text{-}4}$=4.3 Hz, $^2J_{5\beta\text{-}5\alpha}$=$^3J_{5\beta\text{-}6}$=7.1 Hz, 1H, $H_{5\beta}$), 2.15 (td, $^3J_{6\text{-}4}$=$^3J_{6\text{-}5\beta}$=7.1 Hz, $^3J_{6\text{-}5\alpha}$=9.0 Hz, 1H, H_6), 2.60 (dt, $^3J_{4\text{-}5\beta}$=4.3 Hz, $^3J_{4\text{-}5\alpha}$=$^3J_{4\text{-}6}$=7.3 Hz, 1H, H_4), 3.80 (d, $^3J_{3\text{-}2}$=7.8 Hz, 1H, H_3), 5.15 (d, $^3J_{2\text{-}3}$=7.8 Hz, 1H, H_2), 6.71-7.45 (m, 15H, H_{arom}); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 11.7 (C_5), 22.5 (C_6), 31.5 (C_4), 65.4 (C_3), 79.6 (C_2), 125.8 (CH), 126.7 (CH), 127.6 (2 x CH), 128.2 (CH), 128.3 (CH), 128.4 (CH), 133.8 (C_q), 134.0 (C_q), 136.5 (C_q), 158.7 (C_1).

Isomer D: R_f (isohexane/diethyl ether 1:1) 0.37; **^{1}H NMR** (300 MHz, $CDCl_3$): δ 1.05-1.15 (m, 2H, H_5), 2.44 (td, $^3J_{6\text{-}4}$=$^3J_{6\text{-}5\alpha}$=7.1 Hz, $^3J_{6\text{-}5\beta}$=8.8 Hz, 1H, H_6), 3.09 (ddd, $^3J_{4\text{-}5\alpha}$=4.8 Hz, $^3J_{4\text{-}6}$=7.1 Hz, $^3J_{4\text{-}5\beta}$=7.7 Hz, 1H, H_4), 4.51 (d, $^3J_{3\text{-}2}$=7.7 Hz, 1H, H_3), 5.32 (d, $^3J_{2\text{-}3}$=7.7 Hz, 1H, H_2), 6.71-7.45 (m, 15H, H_{arom}); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 9.9 (C_5), 23.7 (C_6), 31.7 (C_4), 66.7 (C_3), 79.7 (C_2), 125.8 (CH), 126.0 (CH), 126.7 (CH), 127.0 (CH), 127.7 (CH), 128.2 (CH), 128.3 (CH), 128.4 (CH), 129.0 (CH), 134.0 (C_q), 134.8 (C_q), 136.5 (C_q), 158.6 (C_1).

(4*R*,5*S*)-3-((1*S*,2*R*)-2-Phenylcyclopropyl)-4,5-diphenyl-2-oxazolidinone (+)-119



$C_{24}H_{21}NO_2$ 355.43 g.mol^{-1}

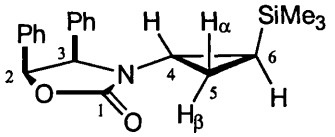
A solution of 3-diethoxymethyl-4,5-diphenyl-2-oxazolidinone **(+)-113** (0.683 g, 2.0 mmol, 1.25 eq) in dry drichloromethane (2.4 mL) was added *via* a motorised syringe pump over 1.5 h to a vigorously stirred mixture of zinc amalgam (1.31 g, 20.0 mmol, 12.5 eq), zinc chloride (1M solution in diethyl ether, 2.0 mL, 2.0 mmol, 1.25 eq), chlorotrimethylsilane (1.27 mL, 10 mmol, 6.25 eq) and styrene (0.167 g, 1.6 mmol, 1 eq) in dry diethyl ether (8.4 mL) under nitrogen at reflux. The mixture was stirred for 2 h and then allowed to cool to room temperature. The reaction was quenched with saturated aqueous $NaHCO_3$ solution (15 mL) and after stirring for 20 min, the mixture was filtered and the separated zinc washed with dichloromethane (15 mL). The organic solvents were removed *in vacuo* and the aqueous layer was extracted with dichloromethane (3 x 15 mL). The combined organic extracts were washed with brine (15 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude product (**(+)-119A:(+)-119B:(+)-119C:(+)-119D**: 56:6:28:6 as determined by ^{1}H NMR) was purified by flash column chromatography (silica, P.E. 40-60°C/diethyl ether 3:2 to 1:1) to give a mixture of cyclopropanes **(+)-119** contaminated by traces of 4,5-diphenyl-*N*-formyl-2-oxazolidinone (mixture of **(+)-119A**, **(+)-119B**, **(+)-119C**, **(+)-119D** 178 mg, 0.5 mmol, 31%, white solid; **(+)-119A** 130 mg, 0.37 mmol, 23%, white solid; 0.87 mmol, 54%).

R_f, IR, ^{1}H and ^{13}C NMR, and mass spectra data of these products were identical to the one given for the corresponding racemate **(±)-119**.

Isomer A: **Mp** 181-183°C (EtOAc/hexane); $[\alpha]_D^{22}$ +135.0 (*c* 0.9, $CHCl_3$); **Anal.** found: C, 80.91; H, 5.92; N, 3.95. Calcd for $C_{24}H_{27}NO_2$: C, 81.10; H, 5.96; N, 3.94.

(±)-4,5-Diphenyl-3-[2-(trimethylsilanyl)-cyclopropyl)]-2-oxazolidinone (±)-120

trans
isomer A



$C_{21}H_{25}NO_2Si$ 351.52 g.mol^{-1}

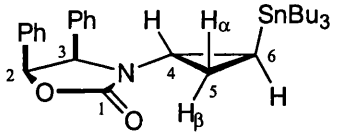
A solution of 3-diethoxymethyl-4,5-diphenyl-2-oxazolidinone **(±)-113** (0.64 g, 1.88 mmol, 1.25 eq) in dry drichloromethane (2.5 mL) was added *via* a motorised syringe pump over 6.5 h to a vigorously stirred mixture of zinc amalgam (1.23 g, 18.8 mmol, 12.5 eq), zinc chloride (1M solution in diethyl ether, 1.88 mL, 1.88 mmol, 1.25 eq), chlorotrimethylsilane (1.19 mL, 9.38 mmol, 6.25 eq) and vinyltrimethylsilane (0.15 g, 1.50 mmol, 1 eq) in dry diethyl ether (7.6 mL) under nitrogen at reflux. The mixture was stirred for 14 h and then allowed to cool to room temperature. Dichloromethane (2 mL) was added and the reaction was quenched with saturated aqueous $NaHCO_3$ solution (20 mL) and after stirring for 20 min, the mixture was filtered through celite and the separated zinc washed with dichloromethane (20 mL). The organic solvents were removed *in vacuo* and the aqueous layer was extracted with dichloromethane (3 x 20 mL). The combined organic extracts were washed with brine (20 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude product **((±)-120A:(±)-120B:(±)-120C:(±)-120D**: 94:<2:<2:<2 as determined by ^{1}H NMR) was purified by flash column chromatography (silica, isohexane/EtOAc 4:1) to give the cyclopropanes **(±)-120** (mixture of **(±)-120A**, **(±)-120B**, **(±)-120C**, **(±)-120D** 0.042 g, 0.12 mmol, 8%, white solid; **(±)-120A** 0.268 g, 0.76 mmol, 51%, white solid; 0.88 mmol, 59%).

Isomer A: **Mp** 145-146°C; R_f (isohexane/EtOAc 4:1) 0.36; **IR** ($CDCl_3$): ν_{max} 3035 (w), 2955 (w), 1734 (s, C=O), 1499 (w), 1455 (w), 1409 (m), 1380 (m), 1247 (w), 1200 (m), 1135 (w), 1025 (w), 991 (w), 898 (w), 834 (s, Si-C), 762 (m), 718 (m), 695 (s) cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$): δ -0.30 (s, 9H, $Si(CH_3)_3$), -0.08 (ddd, $^3J_{6\text{-}4}$=5.0 Hz, $^3J_{6\text{-}5\alpha}$=8.2 Hz, $^3J_{6\text{-}5\beta}$=11.4 Hz, 1H, H_6), 0.87 (ddd, $^2J_{5\alpha\text{-}5\beta}$=4.8 Hz, $^3J_{5\alpha\text{-}4}$=6.2 Hz, $^3J_{5\alpha\text{-}6}$=8.2 Hz, 1H, $H_{5\alpha}$), 1.23 (ddd, $^3J_{5\beta\text{-}4}$=3.2 Hz, $^2J_{5\beta\text{-}5\alpha}$=4.8 Hz, $^3J_{5\beta\text{-}6}$=11.4 Hz, 1H, $H_{5\beta}$), 2.39 (ddd, $^3J_{4\text{-}5\beta}$=3.2 Hz, $^3J_{4\text{-}6}$=5.0 Hz, $^3J_{4\text{-}5\alpha}$=6.2 Hz, 1H, H_4), 4.86 (d, $^3J_{3\text{-}2}$=8.0 Hz, 1H, H_3), 5.78 (d, $^3J_{2\text{-}3}$=8.0 Hz, 1H, H_2), 6.86-7.15 (m, 10H, H_{arom}); **^{13}C NMR** (75 MHz, $CDCl_3$):

δ 5.3 (C_6), 11.5 (C_5), 28.9 (C_4), 66.9 (C_3), 79.6 (C_2), 125.9 (CH), 127.6 (CH), 127.8 (CH), 128.2 (CH), 128.3 (CH), 134.3 (C_q), 134.4 (C_q), 158.5 (C_1); **CI(methane)-MS** *m/z* (%): 352 (MH^+, 100), 308 ($[M+H-CO_2]^+$, 86), 292 ($[M-Ph]^+$, 15), 230 (10), 180 (62), 130 (7), 100 (3), 73 ($SiC_3H_9^+$, 17); **HMRS**: MH^+, found 352.17348. $C_{21}H_{26}NO_2Si$ requires 352.17327; **Anal.** found: C, 71.92; H, 7.18; N, 3.98. Calcd for $C_{21}H_{25}NO_2Si$: C, 71.75; H, 7.17; N, 3.98.

(±)-4,5-Diphenyl-3-[2-(tributylstannanyl)-cyclopropyl)]-2-oxazolidinone (±)-121

trans
isomer A

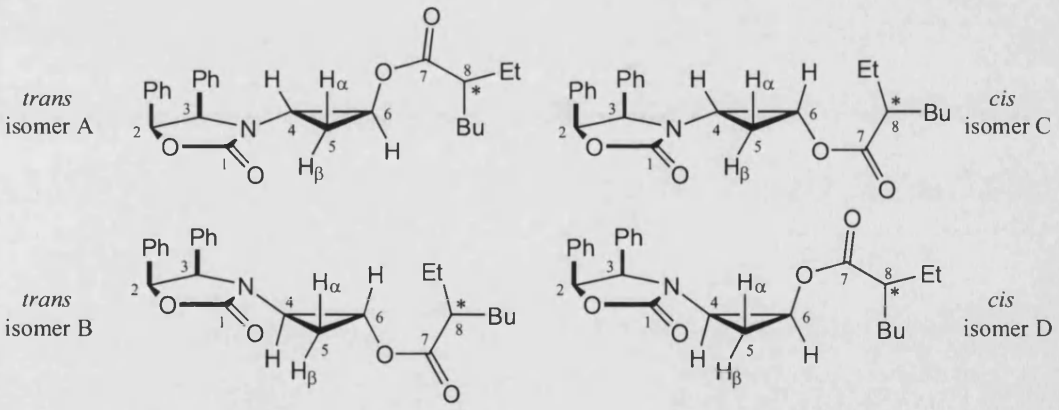


$C_{30}H_{43}NO_2Sn$ 568.37 $g.mol^{-1}$

A solution of 3-diethoxymethyl-4,5-diphenyl-2-oxazolidinone **(±)-113** (0.43 g, 1.25 mmol, 1.25 eq) in dry drichloromethane (1.5 mL) was added *via* a motorised syringe pump over 3 h to a vigorously stirred mixture of zinc amalgam (0.82 g, 12.5 mmol, 12.5 eq), zinc chloride (1M solution in diethyl ether, 1.25 mL, 1.25 mmol, 1.25 eq), chlorotrimethylsilane (0.79 mL, 6.25 mmol, 6.25 eq) and tributyl(vinyl)tin (0.317 g, 1 mmol, 1 eq) in dry diethyl ether (5.25 mL) under nitrogen at reflux. The mixture was stirred for 16 h and then allowed to cool to room temperature. Dichloromethane (2 mL) was added and the reaction was quenched with saturated aqueous $NaHCO_3$ solution (20 mL) and after stirring for 20 min, the mixture was filtered through celite and the separated zinc washed with dichloromethane (20 mL). The organic solvents were removed *in vacuo* and the aqueous layer was extracted with dichloromethane (3 x 20 mL). The combined organic extracts were washed with brine (20 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude product (**(±)-121A:(±)-121B:(±)-121C:(±)-121D**: 94:<2:<2:<2 as determined by ^1H NMR) was purified by flash column chromatography (silica, isohexane/EtOAc 4:1) to give the cyclopropanes **(±)-121** (mixture of **(±)-121A**, **(±)-121B**, **(±)-121C**, **(±)-121D** 11 mg, 0.02 mmol, 2%, yellow oil; **(±)-121A** 0.126 g, 0.22 mmol, 22%, amorphous solid; 0.24 mmol, 24%).

Isomer A: R_f (P.E. 40-60°C/ether 7:3) 0.23; **IR** ($CDCl_3$): ν_{max} 2959 (s), 2923 (s), 2872 (m), 2849 (m), 1748 (s, C=O), 1457 (m), 1374 (m), 1218 (m), 1025 (w), 761 (w), 698 (m) cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 0.02 (ddd, $^3J_{6\text{-}4}$=5.0 Hz, $^3J_{6\text{-}5\alpha}$=8.3 Hz, $^3J_{6\text{-}5\beta}$=11.5 Hz, 1H, H_6), 0.48-0.64 (m, 6H, 3 x CH_2), 0.82 (t, J=7.2 Hz, 9H, 3 x CH_3), 0.90 (ddd, $^2J_{5\alpha\text{-}5\beta}$=5.0 Hz, $^3J_{5\alpha\text{-}4}$=5.9 Hz, $^3J_{5\alpha\text{-}6}$=8.3 Hz, 1H, $H_{5\alpha}$), 1.10-1.33 (m, 13H, 6 x CH_2 and $H_{5\alpha}$), 2.44 (ddd, $^3J_{4\text{-}5\beta}$=3.0 Hz, $^3J_{4\text{-}6}$=5.1 Hz, $^3J_{4\text{-}5\alpha}$=5.9 Hz, 1H, H_4), 4.80 (d, $^3J_{3\text{-}2}$=7.9 Hz, 1H, H_3), 5.73 (d, $^3J_{2\text{-}3}$=7.9 Hz, 1H, H_2), 6.86-6.90 (m, 2H, H_{arom}), 6.94-6.99 (m, 2H, H_{arom}), 7.01-7.11 (m, 6H, H_{arom}); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 0.8 (^1J=172.5 Hz, ^1J=180.7 Hz, C_6), 8.3 (^1J=163.1 Hz, ^1J=170.3 Hz, CH_2), 11.9 (^2J=9.4 Hz, C_5), 13.5 (CH_3), 27.1 (^2J=26.9 Hz, ^2J=28.1 Hz, CH_2), 28.7 (^3J=10.3 Hz, ^3J=17.0 Hz, CH_2), 29.1 (^2J=5.0 Hz, C_4), 65.8 (C_3), 79.7 (C_2), 125.9 (CH), 127.5 (CH), 127.7 (2 x CH), 127.8 (2 x CH), 128.1 (CH), 128.2 (CH), 134.4 (C_q), 134.5 (C_q), 158.4 (C_1); **EI-MS** *m/z* (%): 569 (M^+, 2), 512 ($[M\text{-}C_4H_9]^+$, 64), 398 ($[M\text{-}C_{12}H_{27}]^+$, 3), 332 (6), 288 (9), 234 (32), 180 (100), 143 (6), 91 (11); **HMRS**: MH^+, found 570.23942. $C_{30}H_{44}NO_2Sn$ requires 570.23885.

(±)-2-Ethylhexyl-[2-(2-oxo-4,5-diphenyloxazolidin-3yl)cyclopropyl]carboxylate (±)-122



$C_{26}H_{31}NO_4$ 421.54 $g.mol^{-1}$

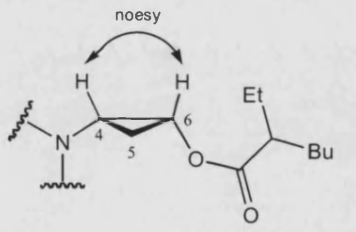
A solution of 3-diethoxymethyl-4,5-diphenyl-2-oxazolidinone **(±)-113** (0.555 g, 1.625 mmol, 1.25 eq) in dry drichloromethane (2 mL) was added *via* a motorised syringe pump over 2.5 h to a vigorously stirred mixture of zinc amalgam (1.09 g, 16.25 mmol, 12.5 eq), zinc chloride (1M solution in diethyl ether, 1.63 mL, 1.63 mmol, 1.25 eq), chlorotrimethylsilane (1.03 mL, 8.125 mmol, 6.25 eq) and vinyl 2-ethylhexanoate

(0.221 g, 1.3 mmol, 1 eq) in dry diethyl ether (6.75 mL) under nitrogen at reflux. The mixture was stirred for 20 h and then allowed to cool to room temperature. Dichloromethane (2 mL) was added and the reaction was quenched with saturated aqueous $NaHCO_3$ solution (20 mL) and after stirring for 20 min, the mixture was filtered through celite and the separated zinc washed with dichloromethane (20 mL). The organic solvents were removed *in vacuo* and the aqueous layer was extracted with dichloromethane (3 x 20 mL). The combined organic extracts were washed with brine (20 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude product (**(±)-122A:(±)-122B:(±)-122C:(±)-122D**: 64:10:13:13 as determined by ^1H NMR) was purified by flash column chromatography (silica, isohexane/EtOAc 9:1 to 4:1) to give the cyclopropanes **(±)-122** (**(±)-122A** 0.237 g, 0.56 mmol, 43%, white solid; mixture of **(±)-122A**, **(±)-122B**, **(±)-122C**, **(±)-122D** 0.118 g, 0.28 mmol, 22%, yellow oil; 0.84 mmol, 65%).

Isomer A (diastereomeric mixture): **Mp** 116-120°C (diethyl ether); R_f (P.E. 30-40°C/EtOAc 4:1) 0.62; **IR** ($CDCl_3$): ν_{max} 2950 (m), 2931 (m), 1742 (s, C=O), 1454 (m), 1518 (m), 1215 (w), 1175 (s), 1022 (w), 762 (m), 696 (m) cm^{-1}; **^1H NMR** (500 MHz, $CDCl_3$): δ 0.50 (t, ^3J=7.5 Hz, 3H, CH_3), 0.66 (t, ^3J=7.5 Hz, 3H, CH_3), 0.68 (t, ^3J=7.5 Hz, 3H, CH_3), 0.75 (t, ^3J=7.5 Hz, 3H, CH_3), 0.77-0.88 (m, 2H, CH_2), 0.91-1.40 (m, 14H, 7 x CH_2), 1.46 (ddd, ^3J=1.8 Hz, ^3J=4.6 Hz, $^3J_{5\beta\text{-}4}$=8.8 Hz, 1H, $H_{5\beta}$), 1.47 (ddd, ^3J=1.8 Hz, ^3J=4.6 Hz, $^3J_{5\beta\text{-}4}$=8.8 Hz, 1H, $H_{5\beta}$), 1.66 (ddd, ^3J=1.7 Hz, ^3J=5.0 Hz, $^3J_{5\alpha\text{-}6}$=7.9 Hz, 1H, $H_{5\alpha}$), 1.67 (ddd, ^3J=1.7 Hz, ^3J=5.0 Hz, $^3J_{5\alpha\text{-}6}$=7.9 Hz, 1H, $H_{5\alpha}$), 2.04 (tt, ^3J=5.2 Hz, ^3J=8.9 Hz, 2H, H_8), 2.27 (ddd, ^3J=1.7 Hz, ^3J=5.0 Hz, $^3J_{4\text{-}5\alpha}$=8.9 Hz, 1H, H_4), 2.28 (ddd, ^3J=1.7 Hz, ^3J=5.0 Hz, $^3J_{4\text{-}5\beta}$=8.9 Hz, 1H, H_4), 4.17 (ddd, ^3J=1.6 Hz, ^3J=4.7 Hz, $^3J_{6\text{-}5\alpha}$=7.9 Hz, 2H, H_6), 5.17 (d, $^3J_{3\text{-}2}$=7.8 Hz, 1H, H_3), 5.18 (d, $^3J_{3\text{-}2}$=7.8 Hz, 1H, H_3), 5.78 (d, $^3J_{2\text{-}3}$=7.8 Hz, 2H, H_2), 6.92-7.08 (m, 20H, H_{arom}); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 11.2 (CH_3), 11.5 (CH_3), 13.6 (CH_3), 13.7 (CH_3), 13.9 (2 x C_5), 14.1 (CH_2), 22.3 (CH_2), 22.4 (CH_2), 25.2 (CH_2), 25.3 (CH_2), 29.0 (CH_2), 29.2 (CH_2), 31.1 (C_4), 31.2 (C_4), 31.5 (CH_2), 31.6 (CH_2), 46.7 (2 x C_8), 52.4 (C_6), 52.5 (C_6), 66.3 (2 x C_3), 79.7 (2 x C_2), 125.8 (CH), 127.7 (CH), 127.8 (CH), 128.1 (4 x CH), 133.7 (2 x C_q), 134.1 (C_q), 134.2 (C_q), 157.4 (2 x C_1), 179.6 (2 x C_7); **CI(methane)-MS** *m/z* (%): 422 (MH^+, 100), 406 ($[M\text{-}CH_3]^+$, 9), 378 ($[M\text{-}C_3H_7]^+$, 54), 338 (12), 294 (27), 278 (15), 250 (25), 234 (55),

180 (21), 145 (7), 127 (10), 99 (9); **HMRS**: MH^+, found 422.23309. $C_{26}H_{32}NO_4$ requires 422.23312.

Isomer B and one *cis* isomer (diastereomeric mixture): R_f (P.E. 30-40°C/EtOAc 4:1) 0.46; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 0.79 (t, ^3J=7.5 Hz, 3H, CH_{3B}), 0.80-0.86 (m, 12H, 2 x CH_{3B} and 2 x CH_{3c}), 0.89-0.95 (m, 9H, 2 x H_{5B} and CH_{3B} and 2 x CH_{2c}), 0.97 (t, ^3J=7.5 Hz, 3H, CH_{3B}), 1.01 (t, ^3J=7.5 Hz, 3H, CH_{3c}), 1.10-1.76 (m, 34H, 9 x CH_{2B} and 8 x CH_{2c}), 2.17 (tt, ^3J=5.5 Hz, ^3J=8.6 Hz, 1H, H_{8B}), 2.18 (tt, ^3J=5.5 Hz, ^3J=8.6 Hz, 1H, H_{8B}), 2.35 (td, ^3J=$^3J_{4\text{-}6}$=5.3 Hz, ^3J=8.7 Hz, 2H, H_{4c}), 2.37-2.43 (m, 2H, H_{8c}), 2.79 (ddd, $^3J_{4\text{-}6}$=1.7 Hz, ^3J=5.2 Hz, ^3J=8.5 Hz, 1H, H_{4B}), 2.80 (ddd, $^3J_{4\text{-}6}$=1.7 Hz, ^3J=5.2 Hz, ^3J=8.5 Hz, 1H, H_{4B}), 3.98 (td, ^3J=4.4 Hz, $^3J_{6\text{-}4}$=5.3 Hz, 1H, H_{6c}), 4.00 (td, ^3J=4.4 Hz, $^3J_{6\text{-}4}$=5.3 Hz, 1H, H_{6c}), 4.23 (td, ^3J=$^3J_{6\text{-}4}$=1.8 Hz, ^3J=4.2 Hz, 1H, H_{6B}), 4.24 (td, ^3J=$^3J_{6\text{-}4}$=1.8 Hz, ^3J=4.2 Hz, 1H, H_{6B}), 4.93 (d, $^3J_{3\text{-}2}$=7.9 Hz, 2H, H_{3B}), 4.97 (d, $^3J_{3\text{-}2}$=7.8 Hz, 2H, H_{3c}), 5.73 (d, $^3J_{2\text{-}3}$=7.8 Hz, 2H, H_{2c}), 5.78 (d, $^3J_{2\text{-}3}$=7.9 Hz, 1H, H_{2B}), 5.79 (d, $^3J_{2\text{-}3}$=7.9 Hz, 1H, H_{2B}), 6.87-7.13 (m, 40H, 20 x CH_B and 20 x CH_c).



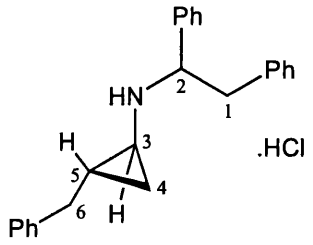
cis isomer

^{13}C NMR (125 MHz, $CDCl_3$): δ 11.6, 11.7, 11.8, 12.0, 12.4 (x2), 14.0 (x3), 22.5 (x2), 22.6, 22.7, 25.1, 25.2, 25.3, 25.5, 27.9 (x2), 29.4, 29.5, 29.6, 29.8, 31.0, 31.4, 31.5, 31.6, 31.8, 46.7, 46.8, 47.2 (x2), 50.5, 52.4 (x2), 60.3, 65.5, 66.6, 79.7, 80.0, 125.8, 125.9, 127.5, 127.8, 127.9 (x2), 128.3, 128.4, 133.8, 134.0, 134.6, 157.9, 158.3, 176.5 (x2), 176.7 (x2).

***Cis* isomer** (diastereomeric mixture): R_f (P.E. 30-40°C/EtOAc 4:1) 0.35; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 0.76 (ddd, $^3J_{5\text{-}6}$=4.3 Hz, $^3J_{5\text{-}4}$=5.3 Hz, $^2J_{5\text{-}5'}$=7.9 Hz, 2H, H_5), 0.88-0.96 (m, 12H, 4 x CH_3), 1.05 (dt, $^3J_{5'\text{-}6}$=7.0 Hz, $^3J_{5'\text{-}4}$=$^2J_{5'\text{-}5}$=8.0 Hz, 1H, $H_{5'}$), 1.06 (dt, $^3J_{5'\text{-}6}$=7.0 Hz, $^3J_{5'\text{-}4}$=$^2J_{5'\text{-}5}$=8.0 Hz, 1H, $H_{5'}$), 1.24-1.39 (m, 8H, 4 x CH_2), 1.45-1.74 (m, 8H, 4 x CH_2), 2.33 (tt, ^3J=5.6 Hz, ^3J=8.4 Hz, 2H, H_8), 2.78 (td, $^3J_{4\text{-}5}$=$^3J_{4\text{-}6}$=5.4 Hz, $^3J_{4\text{-}5'}$=8.7 Hz, 2H, H_4), 4.37 (ddd, $^3J_{6\text{-}5}$=4.3 Hz, $^3J_{6\text{-}4}$=5.4 Hz, $^3J_{6\text{-}5'}$=7.0 Hz, 2H, H_6), 4.83 (d, $^3J_{3\text{-}2}$=7.8 Hz, 1H, H_3), 4.84 (d, $^3J_{3\text{-}2}$=7.8 Hz, 1H, H_3), 5.78 (d, $^3J_{2\text{-}3}$=7.8 Hz, 1H, H_2), 5.79 (d, $^3J_{2\text{-}3}$=7.8 Hz, 1H, H_2), 6.87-7.11 (m, 20H, H_{arom}); **^{13}C NMR** (125 MHz, $CDCl_3$):

δ 11.7 (2 x C_5), 11.8 (2 x CH_3), 13.9 (CH_3), 14.0 (CH_3), 22.6 (CH_2), 22.7 (CH_2), 25.1 (CH_2), 25.3 (CH_2), 28.4 (2 x C_4), 29.5 (CH_2), 29.6 (CH_2), 31.3 (CH_2), 31.6 (CH_2), 47.0 (2 x C_8), 50.6 (2 x C_6), 66.4 (2 x C_3), 80.0 (2 x C_2), 125.9 (2 x CH), 127.4 (CH), 127.9 (CH), 128.0 (CH), 128.3 (CH), 128.4 (CH), 134.1 (2 x C_q), 134.4 (2 x C_q), 158.3 (2 x C_1), 176.1 (C_7), 176.2 (C_7).

(±)-1-(2-Benzylcyclopropyl)-2-pyrrolidinone (±)-123



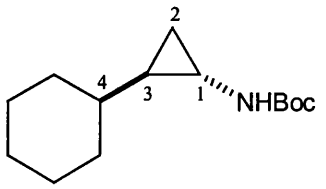
$C_{24}H_{25}N.HCl$ 363.92g.mol^{-1}

A mixture of cyclopropane **(±)-114A** (100 mg, 0.27 mmol, 1 eq), Pd/C (5%, 35 mg, 12.4 μmol, 0.046 eq), absolute ethanol (2.5 mL), THF (2.5 mL) and a solution of hydrochloric acid (5-6M solution in isopropanol, 5 drops) was hydrogenated at 4 bar for 24 h. The reaction mixture was filtered, concentrated *in vacuo* and the residue was taken up in a solution of hydrochloric acid (5-6M solution in isopropanol, 3 mL). The solvent was then evoparated *in vacuo* and the residue triturated in dry diethyl ether (2 mL). The resulting precipitate was filtered, washed with dry diethyl ether (2 mL) to give the *title compound* **(±)-123** (63 mg, 0.18 mmol, 67%) as a white solid.

Mp 214-217°C; **IR** (CH_2Cl_2): ν_{max} 3215 (br, NH), 2960 (m), 1581 (w, C=C), 1456 (m), 1157 (w), 1069 (w), 1039 (w), 771 (w), 746 (m), 737 (m), 698 (s) cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$): δ 0.56-0.64 (m, 1H, H_4), 1.58-1.71 (m, 2H, H_3 and H_4), 1.96-2.03 (m, 1H, H_5), 2.39 (dd, $^3J_{6\text{-}5}$=6.0 Hz, ^2J=14.4 Hz, 1H, H_6), 2.54 (dd, $^3J_{6\text{-}5}$=6.0 Hz, ^2J=14.4 Hz, 1H, H_6), 3.38 (t, $^3J_{1\text{-}2}$=^2J=12.5 Hz, 1H, H_1), 3.90 (dd, $^3J_{1\text{-}2}$=2.5 Hz, ^2J=12.5 Hz, 1H, H_1), 4.01-4.14 (m, 1H, H_2) 6.81-6.96 (m, 4H, H_{arom}), 7.02-7.37 (m, 11H, H_{arom}), 10.23 (br s, 1H, N*H*H$^+$), 10.44 (br s, 1H, NH*H*$^+$); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 11.0 (C_4), 17.3 (C_5), 33.6 (C_3), 36.4 (CH_2), 40.4 (CH_2), 66.5 (C_2), 126.5 (CH), 126.6 (CH), 128.2 (CH), 128.5 (CH), 128.7 (CH), 128.8 (CH), 129.0 (CH), 129.1 (CH), 129.4 (CH), 133.9

(C_q), 135.6 (C_q), 138.6 (C_q); **CI(ammonia)-MS** *m/z* (%): 326 ([M-H-HCl]$^+$, 100), 234 (24), 185 (92), 181 ($C_{14}H_{13}^+$, 20), 153 (36) ; **HMRS**: (M-HCl)$^+$, found 327.19815. $C_{24}H_{25}N$ requires 327.199253.

(±)-*tert*-Butyl *N*-(2-cyclohexylcyclopropyl)carbamate (±)-124



$C_{14}H_{25}NO_2$ 239.36 g.mol^{-1}

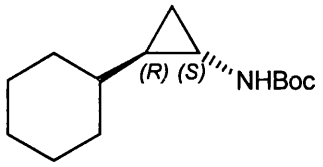
A mixture of cyclopropane **(±)-117A** (200 mg, 0.55 mmol, 1 eq), $Pd(OH)_2/C$ (20%, 52 wt. % water, 200 mg, 0.14 mmol, 0.25 eq), glacial acetic acid (5 mL) and THF (5 mL) was hydrogenated at 4 bar for 6 h, left for 18 h under nitrogen and then hydrogenated at 4 bar for a further 6 h. The reaction mixture was filtered, concentrated *in vacuo* and used in the next step without further purification.

Di-*tert*-butyl dicarbonate (145 mg, 0.66 mmol, 1.2 eq) was added portionwise to a solution of crude amine (0.55 mmol, 1 eq) and triethylamine (0.19 mL, 1.38 mmol, 2.5 eq) in dry dichloromethane (3 mL) under nitrogen. After stirring for 18 h, dichloromethane (10 mL) and brine (5 mL) were added to the reaction mixture. The organic layer was separated and the aqueous layer was extracted with dichloromethane (5 mL). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (silica, P.E. 30-40°C/diethyl ether 9:1 to 8.5/1.5) to give the protected *amine* **124** (84 mg, 0.36 mmol, 65% for the 2 steps) as a yellow oil.

R_f (P.E. 30-40°C/ether 85:15) 0.42; **IR** (film): ν_{max} 3335 (br, NH), 2978 (m), 2924 (s), 2851 (w), 1705 (s, C=O), 1514 (m), 1365 (m), 1171 (m) cm^{-1}; **^{1}H NMR** (500 MHz, 330 K, $CDCl_3$): δ 0.47-0.53 (m, 2H, H_2), 0.59-0.68 (m, 2H, H_3 and H_4), 0.95-1.19 (m, 5H), 1.40 (s, 9H, $C(CH_3)_3$), 1.54-1.71 (m, 4H), 1.84-1.89 (m, 1H), 2.23-2.28 (m, 1H, H_1), 4.54 (br s, 1H, NH); **^{13}C NMR** (125 MHz, 330 K, $CDCl_3$): δ 12.3 (C_2), 26.1 (CH_2), 26.2 (CH_2), 26.5 (CH_2), 27.2 (C_3), 28.4 (C_1 and $C(CH_3)_3$), 32.1 (CH_2), 32.7 (CH_2), 40.7 (C_4), 79.1 ($C(CH_3)_3$), 156.4 (C=O); **CI(methane)-MS** *m/z* (%): 240 (MH$^+$, 36), 184 (100),

140 (41), 57 ($C_4H_9^+$, 36); **HMRS**: MH^+, found 240.19634. $C_{14}H_{26}NO_2$ requires 240.19634.

(+)-*tert*-Butyl *N*-((1*S*,2*R*)-2-cyclohexylcyclopropyl)carbamate (+)-124



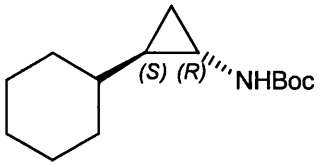
$C_{14}H_{25}NO_2$ 239.36 g.mol^{-1}

A mixture of cyclopropane **(+)-117A** (121 mg, 0.336 mmol, 1 eq), di-*tert*-butyl dicarbonate (146 mg, 0.672 mmol, 2 eq), $Pd(OH)_2/C$ (20%, 52 wt. % water, 71 mg, 0.051 mmol, 0.15 eq) and THF (8.5 mL) was hydrogenated at 5.5 bar at 30°C for 7 h. The reaction mixture was filtered, concentrated *in vacuo* and purified by flash column chromatography (silica, P.E. 30-40°C/diethyl ether 9:1 to 8.5:1.5) to give the *title compound* **(+)-124** (76 mg, 0.317 mmol, 95%) as a white solid.

R_f, IR, ^1H and ^{13}C NMR, and mass spectra data were identical to the one given for the corresponding racemate **(±)-124**.

Mp 64-67°C; $[\alpha]_D^{20}$ +47.0 (*c* 1.32, $CHCl_3$); **Anal.** found: C, 70.08; H, 10.61; N, 5.82. Calcd for $C_{14}H_{25}NO_2$: C, 70.25; H, 10.53; N, 5.83.

(-)-*tert*-Butyl *N*-((1*S*,2*R*)-2-cyclohexylcyclopropyl)carbamate (-)-124



$C_{14}H_{25}NO_2$ 239.36 g.mol^{-1}

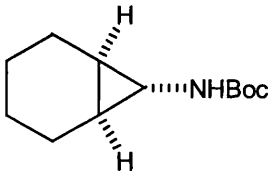
A mixture of cyclopropane **(-)-117A** (122 mg, 0.337 mmol, 1 eq), di-*tert*-butyl dicarbonate (147 mg, 0.675 mmol, 2 eq), $Pd(OH)_2/C$ (20%, 52 wt. % water, 71 mg,

0.051 mmol, 0.15 eq) and THF (8.5 mL) was hydrogenated at 5.5 bar at 30°C for 8 h. The reaction mixture was filtered, concentrated *in vacuo* and purified by flash column chromatography (silica, P.E. 40-60°C/diethyl ether 9:1 to 8.5:1.5) to give the *title compound* **(-)-124** (75 mg, 0.313 mmol, 93%) as a white solid.

R_f, IR, ^1H and ^{13}C NMR, and mass spectra data were identical to the one given for the corresponding racemate **(±)-124**.

Mp 65-67°C; $[\alpha]_D^{20}$ -47.7 (*c* 1.32, $CHCl_3$); **Anal.** found: C, 70.39; H, 10.74; N, 5.82. Calcd for $C_{14}H_{25}NO_2$: C, 70.25; H, 10.53; N, 5.83.

tert-Butyl _N_-(bicyclo[4.1.0]hept-7-yl)carbamate 125



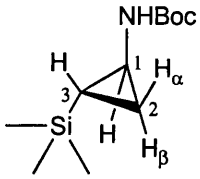
$C_{12}H_{21}NO_2$ 211.30 g.mol^{-1}

A mixture of cyclopropane **(±)-118A** (0.2 g, 0.60 mmol, 1 eq), $Pd(OH)_2/C$ (20%, 52 wt. % water, 0.2 g, 0.14 mmol, 0.25 eq), glacial acetic acid (5 mL) and THF (5 mL) was hydrogenated at 4 bar for 9 hours, left for 18 hours under nitrogen and then hydrogenated at 4 bar hydrogen for a further 9 hours. The reaction mixture was filtered, concentrated *in vacuo* and used in the next step without further purification.
Di-*tert*-butyl dicarbonate (157 mg, 0.72 mmol, 1.2 eq) was added portionwise to a solution of crude amine (0.6 mmol, 1 eq) and distilled triethylamine (0.17 mL, 1.2 mmol, 2 eq) in dry dichloromethane (2.4 mL) under nitrogen. After stirring for 18 hours, dichloromethane (10 mL) and brine (5 mL) were added to the reaction mixture. The organic layer was separated and the aqueous layer was extracted with dichloromethane (5 mL). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (silica, P.E. 30-40°C/diethyl ether 8.5:1.5to 4:1) to give the protected *amine* **125** (74 mg, 0.35 mmol, 58% for the 2 steps) as a white solid.

Alternatively, a mixture of cyclopropane **(+)-118A** (100 mg, 0.3 mmol, 1 eq), di-*tert*-butyl dicarbonate (131 mg, 0.6 mmol, 2 eq), $Pd(OH)_2/C$ (20%, 52 wt. % water, 86 mg, 0.06 mmol, 0.2 eq) and THF (10 mL) was hydrogenated at 5.5 bar at 35°C for 8 h. The reaction mixture was filtered, concentrated *in vacuo* and purified by flash column chromatography (silica, P.E. 40-60°C/diethyl ether 9:1 to 4:1) to give the *title compound* **125** (60 mg, 0.284 mmol, 95%) as a white solid.

Mp 103-104°C (hexane); R_f (P.E. 30-40°C/ether 85:15) 0.38; **IR** ($CDCl_3$): ν_{max} 3340 (br, NH), 2925 (m), 2852 (w), 1682 (s, C=O), 1518 (m), 1366 (m), 1251 (m), 1170 (m), 1143 (m); 1058 (w) cm^{-1}; **^{1}H NMR** (500 MHz, 330 K, $CDCl_3$): δ 0.93-0.96 (m, 2 x CH), 1.04-1.13 (m, 2H), 1.17-1.25 (m, 2H), 1.42 (s, 9H, $C(CH_3)_3$), 1.64-1.71 (m, 2H), 1.80-1.88 (m, 2H), 2.16-2.19 (m, 1H, C*H*NH), 4.53 (br s, 1H, NH); **^{13}C NMR** (125 MHz, 330K, $CDCl_3$): δ 19.4 (2 x CH), 21.5 (2 x CH_2), 22.5 (2 x CH_2), 28.5 ($C(CH_3)_3$), 34.8 (CHNH), 79.1 ($C(CH_3)_3$), 156.6 (C=O); **CI(methane)-MS** *m/z* (%): 212 (MH^+, 92), 184 (18), 156 (94), 138 (15), 112 (92, 110 ($[M\text{-}Boc]^+$, 90), 74 (47), 57 ($C_4H_9^+$, 100); **HMRS**: MH^+, found 212.16589. $C_{12}H_{22}NO_2$ requires 212.16505; **Anal.** found: C, 68.28; H, 10.21; N, 6.66. Calcd for $C_{12}H_{21}NO_2$: C, 68.21; H, 10.02; N, 6.63.

(±)-*tert*-Butyl *N*-[2-(trimethylsilanyl)-cyclopropyl]carbamate (±)-126



$C_{11}H_{23}NO_2Si$ 229.39 $g.mol^{-1}$

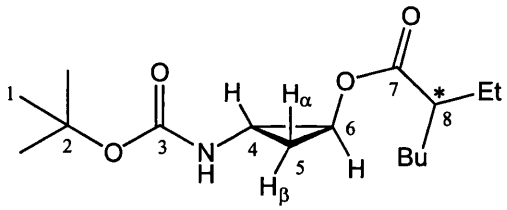
A mixture of cyclopropane **(±)-120A** (200 mg, 0.57 mmol, 1 eq), $Pd(OH)_2/C$ (20%, 52 wt. % water, 200 mg, 0.14 mmol, 0.25 eq), glacial acetic acid (5 mL) and THF (5 mL) was hydrogenated at 4 bar for 9 h, left for 18 h under nitrogen and then hydrogenated at 4 bar for a further 7 h. The reaction mixture was filtered, concentrated *in vacuo* and used in the next step without further purification.

Di-*tert*-butyl dicarbonate (145 mg, 0.66 mmol, 1.2 eq) was added portionwise to a solution of crude amine (maximum 0.57 mmol, 1 eq) and triethylamine (0.19 mL, 1.38 mmol, 2.5 eq) in dry dichloromethane (4 mL) under nitrogen. After stirring for 18 h,

dichloromethane (10 mL) and brine (5 mL) were added to the reaction mixture. The organic layer was separated and the aqueous layer was extracted with dichloromethane (5 mL). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (silica, P.E. 30-40°C/diethyl ether 9:1 to 8.5/1.5) to give the protected *amine* **(±)-126** (28 mg, 0.12 mmol, 21% for the 2 steps) as an amorphous solid.

R_f (P.E. 30-40°C/ether 9:1) 0.35; **IR** (film): ν_{max} 3348 (br, NH), 2956 (m), 1701 (s, C=O), 1406 (w), 1366 (m), 1249 (s), 1172 (s), 1096 (m), 1077 (m), 836 (s, Si-C) cm^{-1}; **^{1}H NMR** (400 MHz, 328 K, $CDCl_3$): δ -0.27 (ddd, $^3J_{3\text{-}1}$=5.0 Hz, $^3J_{3\text{-}2\beta}$=8.0 Hz, $^3J_{3\text{-}2\alpha}$=11.2 Hz, 1H, H_6), -0.05 (s, 9H, $Si(CH_3)_3$), 0.56 (ddd, $^2J_{2\beta\text{-}2\alpha}$=4.6 Hz, $^3J_{2\beta\text{-}1}$=6.5 Hz, $^3J_{2\beta\text{-}3}$=8.0 Hz, 1H, $H_{2\beta}$), 0.67 (ddd, $^3J_{2\alpha\text{-}1}$=3.4 Hz, $^2J_{2\alpha\text{-}2\beta}$=4.6 Hz, $^3J_{2\alpha\text{-}3}$=11.2 Hz, 1H, $H_{2\alpha}$), 1.42 (s, 9H, $C(CH_3)_3$), 2.42-2.48 (m, 1H, H_1), 4.62 (br s, 1H, NH); **^{13}C NMR** (100 MHz, 328 K, $CDCl_3$): δ -2.4 ($Si(CH_3)_3$), 7.0 (C_3), 10.6 (C_2), 27.3 (C_1), 28.5 ($C(CH_3)_3$), 79.2 ($C(CH_3)_3$), 156.5 (C=O); **Positive electrospray-MS** *m/z* (%): 252 (MNa^+, 100), 217 (6); **HMRS**: MNa^+, found 252.13933. $C_{11}H_{23}NNaO_2Si$ requires 252.13903.

(±)-2-Ethylhexyl-[2-(*tert*-butoxycarbonylamino)-cyclopropyl] carboxylate (±)-127



$C_{16}H_{29}NO_4$ 299.41 $g.mol^{-1}$

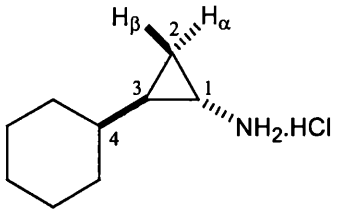
A mixture of cyclopropane **(±)-122A** (19 mg, 0.45 mmol, 1 eq), $Pd(OH)_2/C$ (20%, 52 wt. % water, 190 mg, 0.135 mmol, 0.3 eq), glacial acetic acid (5 mL) and (5 mL) was hydrogenated at 4 bar for 6.5 h, left for 18 h under nitrogen and then hydrogenated at 4 bar for a further 5 h. The reaction mixture was filtered, concentrated *in vacuo* and used in the next step without further purification.

Di-*tert*-butyl dicarbonate (118 mg, 0.54 mmol, 1.2 eq) was added portionwise to a solution of crude amine (0.45 mmol, 1 eq) and triethylamine (0.13 mL, 0.9 mmol, 2 eq)

in dry dichloromethane (3 mL) under nitrogen. After stirring for 16 h, dichloromethane (10 mL) and brine (5 mL) were added to the reaction mixture. The organic layer was separated and the aqueous layer was extracted with dichloromethane (5 mL). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude product was purified twice by flash column chromatography (silica, P.E. 30-40°C/EtOAc 9:1 then DCM/EtOAc 9.5:0.5 to 9:1) to give a diastereomeric mixture of the protected *amine* **(±)-127** contaminated by a small amount of an unidentified by-product (20 mg, 0.067 mmol, 15 %) as an amorphous solid.

R_f (P.E. 30-40°C/ether 4:1) 0.22; **IR** (film): ν_{max} 3371 (br, NH), 2962 (s), 2933 (s), 2862 (m), 1741 (s, C=O), 1711 (s, C=O), 1518 (w), 1460 (m), 1367 (m), 1252 (m), 1167 (s) cm^{-1}; **^{1}H NMR** (diastereomeric mixture, 500 MHz, 330 K, $CDCl_3$): δ 0.83-0.90 (m, 12H, 4 x CH_3), 1.03 (dt, $^3J_{5\beta\text{-}4}$=5.0 Hz, $^2J_{5\beta\text{-}5\alpha}$=7.4 Hz, $^3J_{5\beta\text{-}6}$=7.4 Hz, 2H, $H_{5\beta}$), 1.11 (ddd, $^3J_{5\alpha\text{-}6}$=4.1 Hz, $^2J_{5\alpha\text{-}5\beta}$=7.3 Hz, $^3J_{5\alpha\text{-}4}$=8.5 Hz, 2H, $H_{5\alpha}$), 1.18-1.35 (m, 8H), 1.40-1.69 (m, 8H), 1.43 (s, 18H, H_1), 2.20 (tt, ^3J=5.5 Hz, ^3J=8.5 Hz, 2H, H_8), 2.69 (ddd, $^3J_{4\text{-}6}$=1.8 Hz, $^3J_{4\text{-}5\beta}$=5.0 Hz, $^3J_{4\text{-}5\alpha}$=8.5 Hz, 2H, H_4), 4.03 (ddd, $^3J_{6\text{-}4}$=1.8 Hz, $^3J_{6\text{-}5\alpha}$=4.1 Hz, $^3J_{6\text{-}5\beta}$=7.5 Hz, 1H, H_6), 4.04 (ddd, $^3J_{6\text{-}4}$=1.8 Hz, $^3J_{6\text{-}5\alpha}$=4.1 Hz, $^3J_{6\text{-}5\beta}$=7.5 Hz, 1H, H_6), 4.75 (br s, 2H, NH); **^{13}C NMR** (diastereomeric mixture, 125 MHz, 330 K, $CDCl_3$): δ 11.6 (2 x CH_3), 11.7 (CH_3), 13.8 (CH_3), 15.1 (C_5), 15.2 (C_5), 22.5 (CH_2), 22.6 (2 x CH_2), 25.2 (CH_2), 25.3 (2 x CH_2), 28.4 (C_1), 29.3 (C_4), 29.5 (CH_2), 29.6 (CH_2), 31.5 (2 x CH_2), 47.0 (2 x C_8), 53.8 (2 x C_6), 80.0 (C_2), 156.1 (2 x C_3), 176.6 (C_7), 176.7 (C_7); **CI(methane)-MS** *m/z* (%): 300 (MH^+, 15), 272 ($[M\text{-}C_2H_5]^+$, 4), 244 ($[M+H\text{-}C_4H_9]^+$, 4), 200 ([M-Boc]$^+$, 7), 145 (16), 127 (39), 99 (16), 72 (23); **HMRS**: MH^+, found 300.21748. $C_{16}H_{30}NO_4$ requires 300.21747.

(±)-2-Cyclohexylcyclopropylamine hydrochloride (±)-128

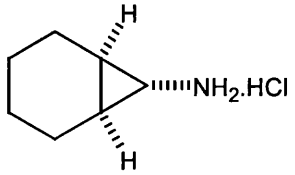


$C_9H_{17}N.HCl$ 175.70 $g.mol^{-1}$

Protected amine **(±)-124** (38 mg, 0.18 mol) in a solution of hydrochloric acid (5-6M solution in isopropanol, 2 mL) was stirred for 10 min. The solvent was removed *in vacuo* and the residue triturated in dry diethyl ether (5 mL). The resulting precipitate was filtered, washed with dry diethyl ether (2 x 4 mL) and dried *in vacuo* to give the *title compound* **(±)-128** (19.5 mg, 0.13 mmol, 74%) as a white solid.

Mp 182-184°C; **IR** (CH_2Cl_2): ν_{max} 2922 (s), 1620 (w), 1520 (w), 1446 (w), 1020 (w) cm^{-1}; **^{1}H NMR** (500 MHz, DMSO): δ0.53 (td, $^3J_{2\beta\text{-}3}=^2J_{2\beta\text{-}2\alpha}$=5.9 Hz, $^3J_{2\beta\text{-}1}$=7.6 Hz, 1H, $H_{2\beta}$), 0.58-0.68 (m, 1H, H_4), 0.81 (ddd, $^3J_{2\alpha\text{-}1}$=3.8 Hz, $^2J_{2\alpha\text{-}2\beta}$=5.7 Hz, $^3J_{2\alpha\text{-}3}$=9.4, 1H, $H_{2\alpha}$), 0.95 (dddd, $^3J_{3\text{-}1}$=3.4 Hz, $^3J_{3\text{-}2\beta}$=6.1 Hz, $^3J_{3\text{-}2\alpha}$=9.4 Hz, $^3J_{3\text{-}4}$=12.8 Hz, 1H, H_3), 0.95-1.20 (m, 5H), 1.50-1.72 (m, 4H), 1.75-1.79 (m, 1H), 2.27 (td, $^3J_{1\text{-}3}=^3J_{1\text{-}2\alpha}$=3.7 Hz, $^3J_{1\text{-}2\beta}$=7.5 Hz, 1H, H_1), 8.37 (br s, 3H, NH_3^+); **^{13}C NMR** (125 MHz, DMSO): δ8.7 (C_2), 23.0 (C_3), 25.5 (2 x CH_2), 25.8 (CH_2), 26.6 (C_1), 31.5 (CH_2), 32.1 (CH_2), 39.4 (C_4); **EI-MS** *m/z* (%): 139 ($[M+H\text{-}HCl]^+$, 2), 110 (4), 96 (5), 82 (7), 67 (5), 56 ($[M\text{-}HCl\text{-}C_6H_{11}]^+$, 100); **HMRS**: $(M+H\text{-}HCl)^+$, found 140.14343. $C_9H_{18}N$ requires 140.14338.

(±)-Bicyclo[4.1.0]hept-7-ylamine hydrochloride 129

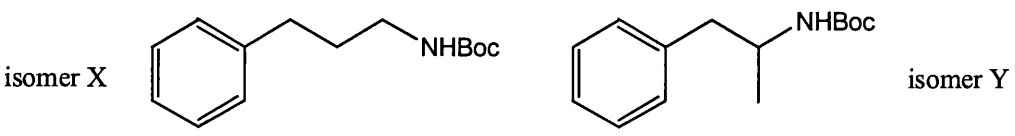


$C_7H_{13}N.HCl$ 147.65 g.mol^{-1}

Protected amine **125** (38 mg, 0.18 mol) in a solution of hydrochloric acid (5-6M solution in isopropanol, 2 mL) was heated with a heat gun for a few seconds in order to dissolve all organic material and then stirred for 10 min. The solvent was removed *in vacuo* and the residue triturated in dry diethyl ether (2 mL). The resulting precipitate was filtered, washed with dry diethyl ether (2 x 4 mL) and dried *in vacuo* to give the *title compound* **129** (19.5 mg, 0.13 mmol, 74%) as a colourless solid.

Mp (decomposition) 225-227°C (lit.,[136] 224-225°C (decomposition)); **IR** (CH_2Cl_2): ν_{max} 3430 (br, NH), 2922 (w), 2855 (w), 1590 (w), 1496 (w), 1160 (w), 1124 (w) cm^{-1}; **^{1}H NMR** (500 MHz, DMSO): δ 1.03-1.20 (m, 4H), 1.21-1.28 (m, 2H), 1.52-1.60 (m, 2H), 1.75-1.84 (m, 2H), 2.23 (br s, 1H, C*H*NH_3^+), 8.23 (br s, 3H, NH_3^+); **^{13}C NMR** (75 MHz, DMSO): δ 15.7 (CH), 21.4 (2 x CH_2), 22.0 (2 x CH_2), 32.9 ($CHNH_3^+$); **EI-MS** *m/z* (%): 111 ([M-HCl]$^+$, 28), 94 (17), 82 (100) 69 (16); **HMRS**: (M-HCl)$^+$, found 111.10458. $C_7H_{13}N$ requires 111.104795.

***tert*-Butyl *N*-(3-phenylpropyl)carbamate 130 and (±)-*tert*-butyl *N*-(1-methyl-2-phenylethyl)carbamate 131**



mixture 3:2

$C_{14}H_{21}NO_2$ 235.32 g.mol^{-1}

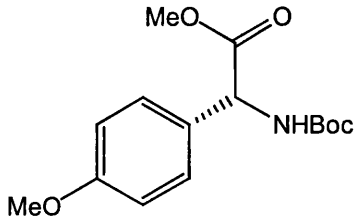
A mixture of cyclopropane **(±)-119A** (136 mg, 0.38 mmol, 1 eq), $Pd(OH)_2/C$ (20%, 52 wt. % water, 136 mg, 0.097 mmol, 0.25 eq), glacial acetic acid (5 mL) and THF (5 mL)

was hydrogenated at 3.5 bar for 7 h, left for 18 h under nitrogen and then hydrogenated at 3.5 bar for a further 8 h. The reaction mixture was filtered, concentrated *in vacuo* and used in the next step without further purification.

Di-*tert*-butyl dicarbonate (100 mg, 0.46 mmol, 1.2 eq) was added portionwise to a solution of crude amine (0.38 mmol, 1 eq) and triethylamine (0.11 mL, 0.76 mmol, 2.5 eq) in dry dichloromethane (2 mL) under nitrogen. After stirring for 18 h, dichloromethane (6 mL) and brine (4 mL) were added to the reaction mixture. The organic layer was separated and the aqueous layer was extracted with dichloromethane (6 mL). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (silica, P.E. 30-40°C/diethyl ether 8.5/1.5) to give a mixture of the *title compounds* **130** and **131** (59 mg, 0.26 mmol, 66% for the 2 steps, **130X:131Y**: 3:2 as determined by ^{1}H NMR) as a white solid.

^{1}H NMR (mixture of isomer X and Y, 500 MHz, $CDCl_3$): δ 1.08 (d, ^3J=6.7 Hz, 3H, CH_{3Y}), 1.42 (s, 9H, $C(CH_3)_{3Y}$), 1.44 (s, 9H, $C(CH_3)_{3X}$), 1.81 (qn, ^3J=7.4 Hz, 2H, $CH_2CH_{2X}CH_2$), 2.62-2.68 (m, 3H, CHH_Y and CH_{2X}), 2.84 (dd, ^3J=5.2 Hz, ^2J=13.3 Hz, 1H, CHH_Y), 3.15 (q, ^3J=6.5 Hz, 2H, $CH_{2X}N$), 3.91 (br s, 1H, CH_YN), 4.39 (br s, 1H, NH_Y), 4.54 (br s, 1H, NH_X), 7.15-7.31 (m, 10H, H_{arom}); **^{13}C NMR** (mixture of isomer X and Y, 125 MHz, $CDCl_3$): δ 20.3 (CH_{3Y}), 28.5 ($C(CH_3)_{3X}$ and $C(CH_3)_{3Y}$), 31.7 (CH_{2X}), 33.1 (CH_{2X}), 40.2 (CH_{2X}), 43.0 (CH_{2Y}), 47.4 (CH_Y), 79.1 ($C(CH_3)_{3X}$ and $C(CH_3)_{3Y}$), 125.9 (CH), 126.3 (CH), 128.3 (CH), 128.4 (CH), 129.5 (CH), 138.2 (C_{qX}), 141.5 (C_{qY}), 155.2 (C=O), 155.9 (C=O).

Methyl (*R*)-2-(*tert*-butoxycarbonyl)amino-2-(4-methoxyphenyl)acetate 133



$C_{15}H_{21}NO_5$ 295.34 g.mol^{-1}

(*R*)-2-*tert*-butoxycarbonylamino-2-(4-hydroxyphenyl)]acetic acid 132

D-4-hydroxyphenylglycine (10.03 g, 60 mmol, 1 eq) and di-*tert*-butyl dicarbonate (18.33 g, 84 mmol, 1.4 eq) was added to a mixture of sodium hydroxide (1M solution in water, 60 mL, 60.0 mmol, 1 eq) and dioxane (60 mL). The reaction mixture was stirred for 4 h and then dioxane was removed *in vacuo*. Diethyl ether (50 mL) was added and the mixture was transferred into a separating funnel. The aqueous layer was separated and acidified to pH 2-3 with solid $KHSO_4$. The mixture was then extracted with EtOAc (3 x 60 mL) and the combined organic extracts were washed with brine (60 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to give **132** (15.13 g, 56.6 mmol, 94%,) as a yellow oil which was used without further purification.

^{1}H NMR (300 MHz, DMSO): δ 1.36 (s, 9H, $C(CH_3)_3$), 3.33 (br s, 1H, OH), 4.93 (d, ^3J=8.2 Hz, 1H, CH), 6.69 (d, ^3J=8.6 Hz, 2H, H_{arom}), 7.15 (d, ^3J=8.6 Hz, 2H, H_{arom}), 7.38 (d, ^3J=8.2 Hz, 1H, NH), 9.42 (br s, 1H, OH); **^{13}C NMR** (75 MHz, DMSO): δ28.1 ($C(CH_3)_3$), 57.0 (CH), 78.1 ($C(CH_3)_3$), 115.0 (CH), 127.5 (CH), 128.8 (CH), 155.0 (C_q), 159.9 (C_q), 172.6 (C=O).

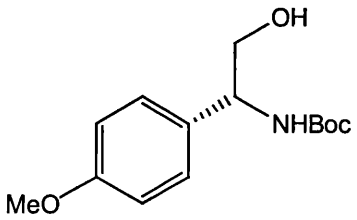
Methyl (*R*)-2-(*tert*-butoxycarbonyl)amino-2-(4-methoxyphenyl)acetate

Anhydrous potassium carbonate (3.1 g, 22.45 mmol, 3 eq) and dimethyl sulfate (1.77 mL, 18.7 mmol, 2.5 eq) was added successively to a solution of crude glycine derivative **132** (2.0 g, 7.48 mmol, 1 eq) in acetone (50 mL) under nitrogen. The reaction mixture was heated at reflux for 4 h and then allowed to cool to room temperature, filtered and concentrated *in vacuo*. The residue was taken up in EtOAc (150 mL) and the organic extract was then washed with an aqueous $NaHCO_3$ solution (5%, 50 mL) and brine (50

mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (silica, P.E. 30-40°C/EtOAc 3:1) to give the *title compound* **133** (1.95 g, 6.6 mmol, 88%) as a white solid.

Mp 82-83°C (lit.,[137] 66-67°C); R_f (P.E. 40-60°C/EtOAc 3:1) 0.35; $[\alpha]_D^{25}$ -145.6 (*c* 1.14, $CHCl_3$) (lit.,[137] $[\alpha]_D^{25}$ -95.3 (*c* 1.2, $CHCl_3$)); **IR** (CH_2Cl_2): ν_{max} 3365 (br, NH), 2955 (m), 1746 (s, C=O), 1714 (s, C=O), 1611 (w, C=C), 1514 (s), 1367 (w), 1249 (m), 1166 (s), 1055 (m), 1031 (m) cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$): δ 1.42 (s, 9H, $C(CH_3)_3$), 3.71 (s, 3H, OCH_3), 3.79 (s, 3H, OCH_3), 5.22-5.27 (m, 1H, CH), 5.48 (br s, 1H, NH), 6.87 (d, ^3J=8.6 Hz, 2H, H_{arom}), 7.27 (d, ^3J=8.6 Hz, 2H, H_{arom}); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 28.3 ($C(CH_3)_3$), 52.6, 55.3, 57.0, 80.1 ($C(CH_3)_3$), 114.3 (CH), 128.4 (CH), 129.0 (CH), 154.8 (C_q), 159.7 (C_q), 171.9 (C=O); **CI(methane)-MS** *m/z* (%): 296 (MH^+, 21), 240 (52), 207 (53), 180 (100), 136 (94), 121 (22); **HMRS**: MH^+, found 296.14985. $C_{15}H_{22}NO_5$ requires 296.14979.

(*R*)-2-(*tert*-butoxycarbonyl)amino-2-(4(methoxyphenyl)ethanol 134

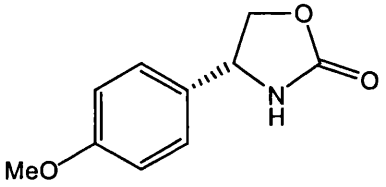


$C_{14}H_{21}NO_4$ 267.32 $g.mol^{-1}$

Anhydrous lithium chloride (1.15 g, 27.09 mmol, 4 eq) and sodium borohydride (1.02 g, 27.09 mmol, 4 eq) was added successively to a solution of ester **133** (2.0 g, 6.77 mmol, 1 eq) in dry THF (30 mL) under nitrogen. The reaction mixture was stirred for 4 h and then cooled to 4°C prior the addition of saturated NH_4Cl solution (10 mL). The mixture was stirred for 30 min and the precipate filtered and washed with EtOAc (20 mL). The organic layer was separated and washed with brine (10 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to give the *title compound* **134** (1.55 g, 5.8 mmol, 86%) as a white solid.

Mp 141-142°C (EtOAc) (lit.,[138] 130-132°C (EtOH/EtOAc); R_f (P.E. 40-60°C/EtOAc 1:1) 0.31; $[\alpha]_D^{25}$ -38.3 (*c* 0.6, $CHCl_3$) (lit.,[138] $[\alpha]_D^{26}$ -38.1 (*c* 1.31, $CHCl_3$); **IR** (CH_2Cl_2): ν_{max} 3372 (br, NH), 2998 (m), 1682 (s, C=O), 1514 (s), 1446 (w), 1245 (m), 1171 (m), 1053 (m), 1031 (m), 739 (m) cm^{-1}; **^{1}H NMR** (500 MHz, 330K, $CDCl_3$): δ 1.38 (s, 9H, $C(CH_3)_3$), 1.91 (br s, 1H, OH), 3.78 (s, 3H, OCH_3), 3.79-3.81 (m, 2H, CH_2OH), 4.67-4.72 (m, 1H, CHN), 5.04 (br s, 1H, NH), 6.86-6.89 (m, 2H, H_{arom}), 7.18-7.22 (m, 2H, H_{arom}); **^{13}C NMR** (125 MHz, 330K, $CDCl_3$): δ 28.4 ($C(CH_3)_3$), 55.3, 56.6, 66.9 (CH_2), 79.9 ($C(CH_3)_3$), 114.4 (CH), 127.8 (CH), 131.8 (CH), 156.1 (C_q), 159.4 (C_q); **CI(methane)-MS** *m/z* (%): 268 (MH^+, 41), 194 (99), 151 (100), 104 (62); **HMRS**: MH^+, found 268.15511 $C_{14}H_{22}NO_4$ requires 268.15488; **Anal.** found: C, 62.75; H, 7.95; N, 5.27. Calcd for $C_{14}H_{21}NO_4$: C, 62.90; H, 7.92; N, 5.24.

(*R*)-4-(4-methoxyphenyl)-2-oxazolidinone 135



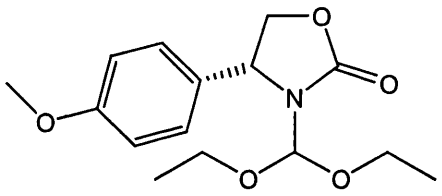
$C_{10}H_{11}NO_3$ 193.20 g.mol^{-1}

Thionyl chloride (0.92 mL, 12.57 mmol, 8 eq) was added dropwise to a solution of alcohol **134** (0.42 g, 1.57 mmol, 1 eq) in dry THF (10.5 mL) under nitrogen at 4°C. The reaction mixture was stirred for a further 10 min at 4 °C and then allowed to warm to room temperature and stirred for 3 h. The reaction mixture was then concentrated *in vacuo* and the crude product purified by flash column chromatography (silica, EtOAc/ P.E. 30-40°C 7:3 to 4:1) to give the *title compound* **135** (0.27 g, 1.4 mmol, 90%) as a white solid.

Mp 149-151°C; R_f (EtOAc/P.E. 40-60°C 4:1) 0.44; $[\alpha]_D^{25}$ -34.0 (*c* 0.5, $CHCl_3$); **IR** (CH_2Cl_2): ν_{max} 3372 (br, NH), 1684 (s, C=O), 1517 (m), 1367 (w), 1245 (m), 1172 (m), 1053 (m), 1032 (m), 668 (s) cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$): δ 3.81 (s, 3H, OCH_3), 4.16 (dd, ^3J=7.0 Hz, ^2J=8.5 Hz, 1H, C*H*HO), 4.70 (t, ^3J=^2J=8.5 Hz, 1H, CH*H*O), 4.91

(dd, ^3J=7.2 Hz, ^2J=8.5 Hz, 1H, CHN), 5.46 (br s, 1H, NH), 6.89-6.95 (m, 2H, H_{arom}), 7.24-7.30 (m, 2H, H_{arom}); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 55.4 (CH_3), 56.0 (CH), 72.7 (CH_2), 114.5 (CH), 127.4 (CH), 131.2 (CH), 159.3 (C_q), 160.0 (C_q); **EI-MS** *m/z* (%): 193 (M^+, 49), 163 (22), 135 (100), 121 (18), 77 (15); **HMRS**: M^+, found 193.07398. $C_{10}H_{11}NO_3$ requires 193.07389; **Anal.** found: C, 62.06; H, 5.84; N, 7.16. Calcd for $C_{10}H_{11}NO_3$: C, 62.17; H, 5.74; N, 7.25.

(*R*)-3-Diethoxymethyl-4-(4-methoxyphenyl)-2-oxazolidinone 136



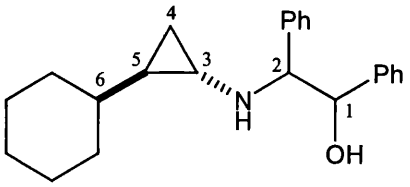
$C_{15}H_{21}NO_5$ 295.33 g.mol^{-1}

A mixture of oxazolidinone **135** (180 mg, 0.93 mmol, 1 eq), aluminium chloride (18.6 mg, 0.14 mmol, 0.15 eq) and triethyl orthoformate (4.6 mL, 27.9 mmol, 30 eq) was heated at 150°C for 36 h. The reaction mixture was cooled to room temperature and then quenched with saturated aqueous $NaHCO_3$ solution (10 mL). The aqueous phase was extracted with diethyl ether (20 mL then 10 mL) and the combined organic extracts were washed with brine (10 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (silica, P.E. 40-60°C/EtOAc 7:3 to 6.5:3.5) to give the *title compound* **136** (73 mg, 0.25 mmol, 26%) as a colourless oil.

R_f (P.E. 40-60°C/EtOAc 6.5:3.5) 0.41; $[\alpha]_D^{22}$ -57.6 (*c* 0.92, CH_2Cl_2); **IR** (film): ν_{max} 2978 (m), 2935 (w), 2910 (w), 1757 (s, C=O), 1662 (m, C=C), 1516 (m), 1248 (m), 1067 (m), 1036 (m), 833 (w), 704 (w) cm^{-1}; **^{1}H NMR** (500 MHz, DMSO): δ 0.68 (t, ^3J=7.1 Hz, 3H, CH_3CH_2), 1.14 (t, ^3J=7.0 Hz, 3H, CH_3CH_2), 3.11 (qd, ^3J=7.1 Hz, ^2J=9.3 Hz, 1H, $CHHCH_3$), 3.27-3.34 (m, 1H, $CHHCH_3$), 3.48-3.59 (m, 2H, CH_2CH_3), 3.72 (s, 3H, OCH_3), 4.63 (dd, ^3J=6.5 Hz, ^2J=8.8 Hz, 1H, $CHHO$), 4.63 (t, ^3J=^2J=8.8 Hz, 1H, $CHHO$), 4.95 (dd, ^3J=6.5 Hz, ^3J=8.8 Hz, CH_2CHN), 5.61 (s, 1H, OCHO), 6.89 (d, ^3J=8.4 Hz, 2H, H_{arom}), 7.27 (d, ^3J=8.4 Hz, 2H, H_{arom}); **^{13}C NMR** (125 MHz, DMSO):

δ 14.0 (CH_2CH_3), 14.7 (CH_2CH_3), 54.6 (CH_2CHN), 55.1 (OCH_3), 61.1 (CH_2CH_3), 61.9 (CH_2CH_3), 70.5 ($CHCH_2O$), 102.1 (OCHO), 113.6 (CH), 128.4 (CH), 132.0 (C_q), 157.2 (C_q), 158.9 (C_q); **EI-MS** *m/z* (%): 295 (M^+, 59), 250 ($[M-C_2H_5O]^+$, 100), 194 (22), 162 (37), 134 (78), 103 (89), 75 (94); **HMRS**: M^+, found 295.14199. $C_{15}H_{21}NO_5$ requires 295.14197.

(±)-2-(2-Cyclohexylcyclopropylamino)-1,2-diphenylethanol (±)-137



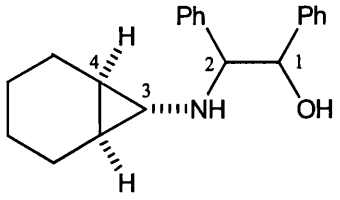
$C_{23}H_{29}NO$ 335.49 g.mol^{-1}

Lithium hydroxide monohydrate (0.745 g, 17.7 mmol, 30 eq) was added in one portion to a suspension of cyclopropane **(±)-117** (0.214 g, 0.59 mmol, 1 eq) in a mixture of absolute ethanol (8 mL) and water (3.5 mL). The reaction mixture was heated at reflux for 48 h and then allowed to cool to room temperature. Most of the ethanol was removed *in vacuo* and saturated aqueous NH_4Cl solution (5 mL) was added to the residue. The aqueous layer was extracted with dichloromethane (3 x 10 mL) and the combined organic extracts were then dried (Na_2SO_4), filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (silica, P.E. 30-40°C/EtOAc 4:1 to 7:3) to give the amino alcohol **(±)-137** (0.155 g, 0.44 mmol, 74%) as a white solid.

Mp 90-92°C; R_f (P.E. 30-40°C/EtOAc 7:3) 0.3; **IR** ($CDCl_3$): ν_{max} 3380 (br), 3028 (w), 2922 (s), 2850 (m), 1495 (m), 1450 (m), 1100 (w), 1053 (w), 1028 (w), 910 (w), 734 (m), 702 (s) cm^{-1}; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 0.23-0.30 (m, 1H, H_4), 0.34-0.42 (m, 1H, H_6), 0.50-0.58 (m, 2H, H_4 and H_5), 0.96-1.18 (m, 5H), 1.57-1.72 (m, 5H), 1.79 (td, $^3J_{3\text{-}4}$=$^3J_{3\text{-}5}$=3.2 Hz, $^3J_{3\text{-}4}$=6.9 Hz, 1H, H_3), 2.07 (br s, 1H), 3.62 (br s, 1H), 4.04 (d, $^3J_{2\text{-}1}$=4.7 Hz, 1H, H_2), 4.91 (d, $^3J_{1\text{-}2}$=4.7 Hz, 1H, H_1), 6.91-6.95 (m, 2H, H_{arom}), 6.98-7.01 (m, 2H, H_{arom}), 7.14-7.24 (m, 6H, H_{arom}); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 12.5 (C_4), 26.1 (CH_2), 26.4 (CH_2), 27.7 (C_5), 32.4 (CH_2), 32.8 (CH_2), 34.3 (C_3), 40.8 (C_6), 68.6 (C_2), 75.2 (C_1), 126.5 (CH), 127.0 (CH), 127.1 (CH), 127.5 (CH), 127.8

(CH), 127.9 (CH), 139.3 (C_q), 140.3 (C_q); **EI-MS** *m/z* (%): 336 (MH^+, 100); **HMRS**: MH^+, found 336.23246. $C_{23}H_{30}NO$ requires 336.23219.

2-(Bicyclo[4.1.0]hept-7-ylamino)-1,2-diphenylethanol 138

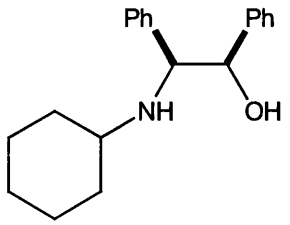


$C_{21}H_{25}NO$ 307.44 g.mol^{-1}

Lithium hydroxide monohydrate (0.566 g, 13.5 mmol, 30 eq) was added in one portion to a suspension of cyclopropane **118** (0.15 g, 0.45 mmol, 1 eq) in a mixture of absolute ethanol (7 mL) and water (3 mL). The reaction mixture was heated at reflux for 24 h and then allowed to cool to room temperature. Most of the ethanol was removed *in vacuo* and saturated aqueous NH_4Cl solution (5 mL) was added to the residue. The aqueous layer was extracted with dichloromethane (3 x 10 mL) and the combined organic extracts were then dried (Na_2SO_4), filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (silica, DCM/MeOH 96:4) to give the amino alcohol **138** (0.116 g, 0.38 mmol, 84%) as a white solid.

Mp 154-156°C; R_f (P.E. 30-40°C/EtOAc 1:1) 0.4; **IR** ($CDCl_3$): ν_{max} 3427 (br), 2987 (m), 2926 (w), 1660 (m), 1541 (w), 735 (m), 702 (s) cm^{-1}; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 0.81-0.87 (m, 2H, H_4), 0.88-0.99 (m, 2H), 1.03-1.07 (m, 2H), 1.36-1.49 (m, 2H), 1.64-1.72 (m, 1H), 1.67 (t, $^3J_{3\text{-}4}$=3.4 Hz, 1H, H_3), 1.76-1.83 (m, 1H), 3.97 (d, $^3J_{2\text{-}1}$=5.4 Hz, 1H, H_2), 4.89 (d, $^3J_{1\text{-}2}$=5.4 Hz, 1H, H_1), 6.99-7.02 (m, 2H, H_{arom}), 7.03-7.06 (m, 2H, H_{arom}), 7.16-7.23 (m, 6H, H_{arom}); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 18.9 (C_4), 19.0 (C_4), 21.5 (CH_2), 21.6 (CH_2), 22.6 (CH_2), 22.8 (CH_2), 41.1 (C_3), 69.1 (C_2), 75.3 (C_1), 125.9 (CH), 126.6 (CH), , 127.3 (CH), 127.4 (CH), 127.8 (CH), 128.0 (CH), 128.2 (CH), 139.4 (C_q), 140.4 (C_q); **EI-MS** *m/z* (%): 307 (M^+, 3), 200 (100), 149 (15), 117 (12), 106 (52), 91 (100), 77 (37), 67 (21), 55 (16); **HMRS**: M^+, found 307.19268. $C_{21}H_{25}NO$ requires 307.19307.

2-Cyclohexylamino-1,2-diphenylethanol 139

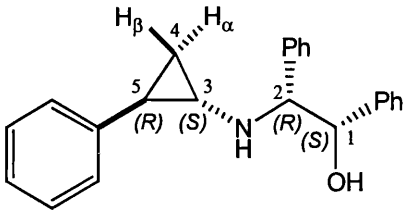


$C_{20}H_{25}NO$ 295.42 $g.mol^{-1}$

A mixture of *trans*-stilbene oxide (1.42 g, 7.23 mmol, 1 eq) and cyclohexylamine (4.15 mL, 36.15 mmol, 5 eq) in methanol (15 mL) was heated at reflux for 60 h. The reaction mixture was cooled to room temperature and then concentrated *in vacuo*. The residue was triturated in hexane and the resulting precipitate was filtered and then with hexane (2 x 10 mL) to give the *title compound* **139** (1.96 g, 6.66 mmol, 92%) as a white solid.

Mp 164-166°C (lit.,[139] 163-164°C (EtOH)); R_f (EtOAc) 0.5; **IR** (CH_2Cl_2): ν_{max} 3390 (br), 3290 (br), 2920 (w), 2852 (w), 1653 (m), 1055 (s), 730 (m) cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$): δ 0.92-1.22 (m, 5H), 1.42-1.79 (m, 4H), 1.82-1.99 (m, 1H), 2.27-2.41 (m, 1H), 3.40 (br s, 1H), 4.13 (d, ^3J=5.2 Hz, 1H, PhC*H*NH), 4.80 (d, ^3J=5.2 Hz, 1H, PhC*H*OH), 6.95-7.12 (m, 4H, H_{arom}), 7.13-7.41 (m, 6H, H_{arom}); **^{13}C NMR** (75 MHz, $CDCl_3$): δ24.6 (CH_2), 25.0 (CH_2), 26.0 (CH_2), 33.0 (CH_2), 34.5 (CH_2), 53.2 (CH), 65.0 (PhCHNH), 76.1 (PhCHOH), 126.7 (CH), 127.4 (CH), 127.8 (CH), 128.0 (CH), 139.6 (C_q), 140.4 (C_q); **EI-MS** *m/z* (%): 296 (MH^+, 15), 188 (100), 106 (63), 91 (8), 77 (Ph^+, 17); **HMRS**: MH^+, found 296.20200. $C_{20}H_{26}NO$ requires 296.20143.

(1*S*,2*R*)-1,2-diphenyl-2-((1*S*,2*R*)-2-phenylcyclopropylamino)ethanol (+)-140



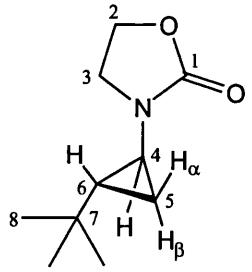
$C_{23}H_{23}NO$ 329.44 g.mol^{-1}

Potassium trimethylsilanolate (90% pure, 323 mg, 2.52 mmol, 8 eq) was added to a solution of cyclopropane **(+)-119A** (112 mg, 0.315 mmol, 1 eq) in dry THF (1.6 mL) under nitrogen. The reaction mixture was heated at 60°C for 3.5 h and, as the reaction was not complete (as determined by TLC), additional potassium trimethylsilanolate (90% pure, 81 mg, 0.63 mmol, 2 eq) was added. The mixture was heated for a further 30 min and then allowed to cool to room temperature. EtOAc (10 mL) and water (5 mL) were added and the mixture was transfered into a separating funnel. The organic layer was separated and the aqueous layer was extracted with EtOAc (5 mL). The combined organic extracts were washed with brine (5 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (silica, P.E. 40-60°C/EtOAc 4:1 to 7:3) to give the *amino alcohol* **(+)-140** (73 mg, 0.22 mmol, 70%) as a white solid.

Mp 138-141°C; R_f (P.E. 30-40°C/EtOAc 7:3) 0.26; $[\alpha]_D^{32}$ +22.0 (*c* 1.0, $CHCl_3$); **IR** ($CHCl_3$): ν_{max} 3405 (br), 3066 (w), 3018 (m), 1558 (m), 1499 (m), 1051 (w), 1028 (w), 734 (m), 762 (s), 700 (m), 669 (m) cm^{-1}; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 0.92 (ddd, $^3J_{4\beta\text{-}5}$=5.3 Hz, $^2J_{4\beta\text{-}4\alpha}$=5.8 Hz, $^3J_{4\beta\text{-}3}$=7.1 Hz, 1H, $H_{4\beta}$), 1.05 (ddd, $^3J_{4\alpha\text{-}3}$=4.2 Hz, $^2J_{4\alpha\text{-}4\beta}$=5.2 Hz, $^3J_{4\alpha\text{-}5}$=9.3 Hz, 1H, $H_{4\alpha}$), 1.90 (ddd, $^3J_{5\text{-}3}$=3.1 Hz, $^3J_{5\text{-}4\beta}$=5.8 Hz, $^3J_{5\text{-}4\alpha}$=9.2 Hz, 1H, H_5), 2.24 (ddd, $^3J_{3\text{-}5}$=3.1 Hz, $^3J_{3\text{-}4\alpha}$=4.2 Hz, $^3J_{3\text{-}4\beta}$=7.2 Hz, 1H, H_3), 3.00 (br s, 2H, OH and NH), 4.08 (d, $^3J_{2\text{-}1}$=5.3 Hz, 1H, H_2), 4.93 (d, $^3J_{1\text{-}2}$=5.3 Hz, 1H, H_1), 6.83-7.31 (m, 15H, H_{arom}); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 16.8 (C_4), 25.4 (C_5), 39.3 (C_3), 69.1 (C_2), 75.6 (C_1), 125.5 (CH), 125.9 (CH), 126.6 (CH), 127.5 (CH), 127.8 (CH), 128.0 (CH), 128.1 (CH), 128.2 (CH), 139.1 (C_q), 140.2 (C_q), 141.7 (C_q); **EI-MS**

m/z (%): 329 (M^+, 6) 222 (100), 132 (52), 117 (98), 91 (Bn^+, 86), 77 (Ph^+, 32); **HMRS**: MH^+, found 329.17795. $C_{23}H_{23}NO$ requires 329.17742.

3-(2-*tert*-Butylcyclopropyl)-2-oxazolidinone 141



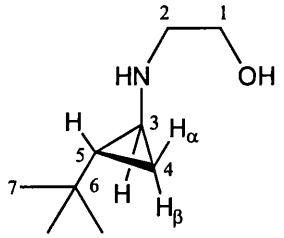
$C_{10}H_{17}NO_2$ 183.25 g.mol^{-1}

A solution of *N*-diethoxymethyl-2-oxazolidinone **108** (0.946 g, 5.0 mmol, 1 eq) in dry diethyl ether (8 mL) was added *via* a motorised syringe pump over 3.45 h to a vigorously stirred mixture of zinc amalgam (3.27 g, 50 mmol, 10 eq), zinc chloride (1M solution in diethyl ether, 5 mL, 5 mmol, 1 eq), chlorotrimethylsilane (3.17 mL, 25 mmol, 5 eq) and 3,3-dimethylbut-1-ene (3.24 mL, 25 mmol, 5 eq) in dry diethyl ether (27 mL) under nitrogen at reflux. The mixture was stirred for 16 h and then allowed to cool to room temperature. The reaction was quenched with saturated saturated $NaHCO_3$ solution (40 mL) and after stirring for 20 min, the mixture was filtered through celite and the separated zinc washed with diethyl ether (3 x 10 mL). The organic layer was separated and the aqueous layer was extracted with diethyl ether (2 x 40 mL). The combined organic extracts were washed with brine (40 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude product (*trans*/*cis*: >95:<5 as determined by ^{1}H NMR) was purified by flash column chromatography (silica, P.E. 30-40°C/EtAOc 1:1) to give almost exclusively the *trans* cyclopropane **141** (0.425 g, 2.32 mmol, 46%) as a yellow oil.

R_f (P.E. 40-60°C/EtOAc 1:1) 0.36; **IR** (film): ν_{max} 2958 (m), 2869 (s), 1755 (s, C=O), 1482 (w), 1423 (m), 1223 (w), 1094 (w), 1039 (m), 765 (m) cm^{-1}; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 0.75 (dt, $^2J_{5\beta\text{-}5\alpha}$=5.9 Hz, $^3J_{5\beta\text{-}4}$=$^3J_{5\beta\text{-}6}$=7.2 Hz, 1H, $H_{5\beta}$), 0.80 (ddd, $^3J_{5\alpha\text{-}4}$=3.7 Hz, $^2J_{5\alpha\text{-}5\beta}$=5.9 Hz, $^3J_{5\alpha\text{-}6}$=9.7 Hz, 1H, $H_{5\alpha}$), 0.85 (s, 9H, H_8), 0.95 (ddd, $^3J_{6\text{-}4}$=3.7 Hz, $^3J_{6\text{-}5\beta}$=7.2 Hz, $^3J_{6\text{-}5\alpha}$=9.8 Hz, 1H, H_6), 2.35 (td, $^3J_{4\text{-}5\alpha}$=$^3J_{4\text{-}6}$=3.7 Hz, $^3J_{4\text{-}5\beta}$=7.3 Hz, 1H,

H_4), 3.45-3.50 (m, 2H, H_3), 4.22 (dt, $^3J_{2\text{-}3}$=3.1 Hz, $^3J_{2\text{-}3}$=^2J=8.0 Hz, 2H, H_2); **^{13}C NMR** (125 MHz, $CDCl_3$): δ9.4 (C_5), 28.2 (C_8), 28.7 (C_7), 29.0 (C_4), 30.6 (C_6), 45.8 (C_3), 61.6 (C_2), 158.4 (C_1); **EI-MS** *m/z* (%): 183 (M^+, 7), 168 ($[M\text{-}CH_3]^+$, 6), 127 ($[M+H\text{-}C_4H_9]^+$, 100), 114 (31), 82 (18), 70 (31), 55 (43), 49 (12), 42 (CH_2=C=O, 60); **HMRS**: MH^+, found 184.13305. $C_{10}H_{18}NO_2$ requires 184.13321.

2-(2-*tert*-Butylcyclopropylamino)ethanol 142

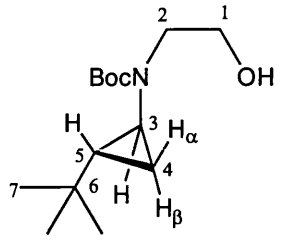


$C_9H_{19}NO$ 157.25 g.mol^{-1}

Lithium hydroxide monohydrate (1.24 g, 29.5 mmol, 30 eq) was added in one portion to a suspension of cyclopropane **141** (0.18 g, 0.98 mmol, 1 eq) in a mixture of absolute ethanol (14 mL) and water (6 mL). The reaction mixture was heated at reflux for 20 h and then allowed to cool to room temperature. Most of the ethanol was removed *in vacuo* and saturated aqueous NH_4Cl solution (5 mL) was added to the residue. The aqueous layer was extracted with dichloromethane (2 x 10 mL then 2 x 5 mL) and the combined organic extracts were dried (Na_2SO_4), filtered and concentrated *in vacuo* to give the amino alcohol **142** (75 mg, 0.48 mmol, 49%) as a yellow oil.

IR (film): ν_{max} 3300 (br), 2953 (s), 2866 (m), 1468 (m), 1387 (m), 1364 (m), 1068 (m), 1043 (m) cm^{-1}; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 0.34-0.41 (m, 2H, H_4), 0.59 (ddd, $^3J_{5\text{-}3}$=3.5 Hz, $^3J_{5\text{-}4\beta}$=6.2 Hz, $^3J_{5\text{-}4\alpha}$=9.9 Hz, 1H, H_5), 0.77 (s, 9H, H_7), 1.95 (td, $^3J_{3\text{-}4\alpha}$=$^3J_{3\text{-}5}$=3.5 Hz, $^3J_{3\text{-}4\beta}$=7.2 Hz, 1H, H_3), 2.71-2.77 (m, 2H, H_2), 2.90 (br s, 3H, OH and NH_2), 3.57 (t, $^3J_{1\text{-}2}$=5.5 Hz, 2H, H_1); **^{13}C NMR** (100 MHz, $CDCl_3$): δ9.4 (C_4), 28.5 (C_7), 28.9 (C_6), 31.8 (C_5), 33.3 (C_3), 51.1 (C_2), 60.5 (C_1); **CI(methane)-MS** *m/z* (%): 158 (MH^+, 100), 100 ($[M\text{-}C_4H_9]^+$, 86); **HMRS**: MH^+, found 158.154382. $C_9H_{20}NO$ requires 158.15448.

tert-Butyl *N*-[(2-*tert*-butylcyclopropyl)-(2-hydroxyethyl)]carbamate 143

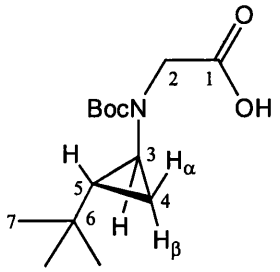


$C_{14}H_{27}NO_4$ 257.37 g.mol^{-1}

Di-*tert*-butyl dicarbonate (106 mg, 0.49 mmol, 1.2 eq) was added portionwise to a solution of amino alcohol **142** (64 mg, 0.407 mmol, 1 eq) and triethylamine (0.07 mL, 0.51 mmol, 1.25 eq) in dry dichloromethane (2 mL) under nitrogen. After stirring for 24 h, the reaction mixture was concentrated *in vacuo*. The crude product was purified by flash column chromatography (silica, P.E. 30-40°C/EtOAc 4:1 to 3:1) to give the *title compound* **143** (76 mg, 0.295 mmol, 72%) as a colourless oil.

***R*$_f$** (P.E. 30-40°C/EtOAc 4:1) 0.29; **IR** (film): ν_{max} 3450 (br, OH), 2955 (s), 2870 (m), 1685 (s, C=O), 1387 (m), 1365 (m), 1180 (m), 1149 (m), 1059 (m) cm^{-1}; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 0.65 (ddd, $^3J_{4\alpha\text{-}3}$=3.9 Hz, $^2J_{4\alpha\text{-}4\beta}$=5.8 Hz, $^3J_{4\alpha\text{-}5}$=9.7 Hz, 1H, $H_{4\alpha}$), 0.71 (ddd, $^2J_{4\beta\text{-}4\alpha}$=5.8 Hz, $^3J_{4\beta\text{-}5}$=6.9 Hz, $^3J_{4\beta\text{-}3}$=7.4 Hz, 1H, $H_{4\beta}$), 0.82 (s, 9H, H_7), 0.85 (ddd, $^3J_{5\text{-}3}$=3.9 Hz, $^3J_{5\text{-}4\beta}$=6.7 Hz, $^3J_{5\text{-}4\alpha}$=10.1 Hz, 1H, H_5), 1.42 (s, 9H, $OC(CH_3)_3$), 2.45 (td, $^3J_{3\text{-}4\alpha}$=$^3J_{3\text{-}5}$=3.8 Hz, $^3J_{3\text{-}4\beta}$=7.5 Hz, 1H, H_3), 3.29 (ddd, $^3J_{2\text{-}1}$=4.6 Hz, $^3J_{2\text{-}1}$=6.2 Hz, ^2J=14.6 Hz, 1H, H_2), 3.41 (ddd, $^3J_{2\text{-}1}$=4.5 Hz, $^3J_{2\text{-}1}$=6.5 Hz, ^2J=14.5 Hz, 1H, H_2), 3.57 (t, $^3J_{1\text{-}2}$=5.5 Hz, 2H, H_1); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 12.2 (C_4), 28.4 (C_7 and $OC(CH_3)_3$), 29.1 (C_6), 32.1 (C_5), 32.2 (C_3), 50.7 (C_2), 62.4 (C_1), 80.1 ($OC(CH_3)_3$), 158.2 (C=O); **CI(ammonia)-MS** *m/z* (%): 256 ([M-H]$^+$, 100), 200 ([M-C_4H_9]$^+$, 30), 182 (32), 156 ([M-Boc]$^+$, 45), 147 (65), 138 (29); **HMRS**: (M-H)$^+$, found 256.191464. $C_{14}H_{26}NO_4$ requires 256.19126.

[*tert*-Butoxycarbonyl-(2-*tert*-butylcyclopropyl)-amino]acetic acid 144

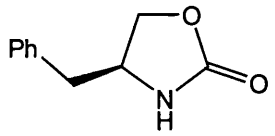


$C_{14}H_{25}NO_4$ 271.36 g.mol^{-1}

Aqueous solution of sodium hydroxide (0.5M in water, 2.2 mL, 1.1 mmol, 4 eq) and potassium permanganate (0.65M in water, 1.7 mL, 1.1 mmol, 4 eq) were added successively to a solution of alcohol **143** (70 mg, 0.27 mmol, 1 eq) in *tert*-butanol (2.7 mL). The reaction mixture was stirred for 24 h and then quenched with sodium thiosulfate (5% in water, 7.75 mL). Diethyl ether (10 mL) was added and the mixture was transferred into a separating funnel. The aqueous layer was separated and then acidified to pH 2 with an aqueous hydrochloric acid solution (1M) at 4°C. The mixture was then extracted with EtOAc (3 x 10 mL) and the combined organic extracts were dried (Na_2SO_4), filtered and concentrated *in vacuo* to give the *title compound* **144** (62 mg, 0.23 mmol, 84%) as a white amorphous solid.

IR (film): ν_{max} 3450 (br, OH), 2954 (m), 1699 (s, C=O), 1385 (m), 1367 (m), 1153 (m), cm^{-1}; **^{1}H NMR** (500 MHz, 328K, $CDCl_3$): δ 0.71 (ddd, $^3J_{4\alpha\text{-}3}$=3.9 Hz, $^2J_{4\alpha\text{-}4\beta}$=5.7 Hz, $^3J_{4\alpha\text{-}5}$=9.7 Hz, 1H, $H_{4\alpha}$), 0.75 (ddd, $^2J_{4\beta\text{-}4\alpha}$=5.7 Hz, $^3J_{4\beta\text{-}5}$=6.6 Hz, $^3J_{4\beta\text{-}3}$=7.3 Hz, 1H, $H_{4\beta}$), 0.84 (s, 9H, H_7), 0.87 (ddd, $^3J_{5\text{-}3}$=3.9 Hz, $^3J_{5\text{-}4\beta}$=6.7 Hz, $^3J_{5\text{-}4\alpha}$=10.1 Hz, 1H, H_5), 1.44 (s, 9H, $OC(CH_3)_3$), 2.59 (td, $^3J_{3\text{-}4\alpha}$=$^3J_{3\text{-}5}$=3.9 Hz, $^3J_{3\text{-}4\beta}$=7.5 Hz, 1H, H_3), 3.83 (d, ^2J=17.7 Hz, 1H, H_2), 4.04 (d, ^2J=17.7 Hz, 1H, H_2), 8.73 (br s, 1H, OH); **^{13}C NMR** (125 MHz, 328K, $CDCl_3$): δ 12.2 (C_4), 28.4 (C_7 and $OC(CH_3)_3$), 29.0 (C_6), 32.3 (C_5), 32.5 (C_3), 50.0 (C_2), 80.7 ($OC(CH_3)_3$), 156.7 (C=O), 175.3 (C_1); **CI(methane)-MS** *m/z* (%): 272 (MH^+, 33), 216 ($[M\text{-}C_4H_9]^+$, 92), 172 ($[M+H\text{-}Boc]^+$, 52), 154 (100); **HMRS**: MH^+, found 272.18676. $C_{14}H_{26}NO_4$ requires 272.18617.

(*S*)-4-Benzyl-2-oxazolidinone 145

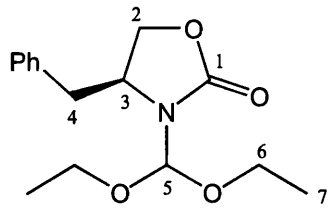


$C_{10}H_{11}NO_2$ 177.20 g.mol^{-1}

A solution of triphosgene (2.05 g, 6.9 mmol, 0.35 eq) in dry dichloromethane (10 mL) was added dropwise over 1 h to a suspension of L-phenylalaninol (3.0 g, 19.71 mmol, 1 eq) and triethylamine (6.04 mL, 43.36 mmol, 2.2 eq) in dry dichloromethane (40 mL) under nitrogen at 4°C. The reaction mixture was stirred for a further hour at 4 °C and then allowed to warm to room temperature and stirred for 2 h. Saturated aqueous NH_4Cl solution (25 mL) and dichloromethane (50 mL) mixture were added to the reaction and after stirring for 20 min, the mixture was transfered into a separating funnel. The aqueous layer was separated and the organic layer washed with saturated aqueous $NaHCO_3$ solution (25 mL) and brine (25 mL). The combined organic extracts were then dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude product was recrystallised from EtOAc/hexane to give the *title compound* **145** (2.60 g, 19.2 mmol, 75%) as a white solid.

Mp 85-86°C (EtOAc/hexane) (lit.,[140] 85-87°C (EtOAc/hexane)); R_f (EtOAc) 0.6; $[\alpha]_D^{17}$ -56.0 (*c* 1.0, $CHCl_3$) (lit.,[140] $[\alpha]_D^{25}$ -62.0 (*c* 1.0, $CHCl_3$)); **IR** ($CHCl_3$): ν_{max} 3285 (br, NH), 3018 (m), 1755 (s, C=O), 1404 (m), 1216 (s), 1032 (w), 756 (s), 702 (w), 667 (m) cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$): δ2.86 (d, ^3J=^2J=6.6 Hz, 2H, CH_2Ph), 4.01-4.11 (m, 1H, CHN), 4.12 (dd, ^3J=5.5 Hz, ^2J=8.3 Hz, 1H, C*H*HO), 4.42 (t, ^3J=^2J=8.3 Hz, 1H, CH*H*O), 5.67 (br s, 1H, NH), 7.13-7.18 (m, 2H, H_{arom}), 7.21-7.35 (m, 3H, H_{arom}); **^{13}C NMR** (75 MHz, $CDCl_3$): δ41.4 (CH_2Ph), 53.8 (CHN), 69.6 (CH_2O), 127.2 (CH), 129.0 (CH), 135.9 (C_q), 159.3 (C=O); **EI-MS** *m/z* (%): 177 (MH^+, 100), 91 (Bn^+, 66).

(*S*)-4-Benzyl-3-diethoxymethyl-2-oxazolidinone 146

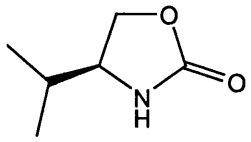


$C_{15}H_{21}NO_4$ 279.34 g.mol^{-1}

A mixture of oxazolidinone **145** (500 mg, 2.82 mmol, 1 eq), aluminium chloride (56 mg, 0.42 mmol, 0.15 eq) and triethyl orthoformate (14 mL, 84.6 mmol, 30 eq) was heated at 155°C for 24 h. The reaction mixture was cooled to room temperature and then quenched with saturated aqueous $NaHCO_3$ solution (10 mL). The aqueous phase was extracted with diethyl ether (20 mL then 10 mL) and the combined organic extracts were washed with brine (10 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (silica, P.E. 30-40°C/EtOAc 8.5:1.5 to 4:1) to give the *title compound* **146** (195 mg, 0.70 mmol, 25%) as a colourless oil.

R_f (P.E. 40-60°C/EtOAc 4:1) 0.35; $[\alpha]_D^{26}$ + 50.4 (*c* 2.58, CH_2Cl_2); **IR** (film): ν_{max} 2978 (m), 2935 (w), 2903 (w), 1759 (s, C=O), 1410 (m), 1236 (m), 1065 (s), 748 (m), 702 (m) cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$): δ 1.22 (t, $^3J_{7\text{-}6}$=7.0 Hz, 3H, H_7), 1.24 (t, $^3J_{7\text{-}6}$=7.0 Hz, 3H, H_7), 2.58-2.67 (m, 1H, H_4), 3.44-3.75 (m, 5H, H_6 and H_4), 3.97 (t, $^3J_{2\text{-}3}$=^2J=8.0 Hz, 1H, H_2), 4.02 (t, $^3J_{2\text{-}3}$=^2J=8.0 Hz, 1H, H_2), 4.14-4.25 (m, 1H, H_3), 5.79 (s, 1H, H_5), 7.10-7.29 (m, 5H, H_{arom}); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 14.6 (C_7), 14.7 (C_7), 39.5 (C_4), 52.8 (C_3), 62.3 (C_6), 67.1 (C_2), 102.3 (C_5), 126.6 (CH), 128.4 (CH), 128.8 (CH), 136.0 (C_q), 157.2 (C_1); **Positive electrospray-MS** *m/z* (%): 302 (MNa^+, 100), 234 ($[M\text{-}C_2H_5O]^+$, 37), 220 (13); **HMRS**: MNa^+, found 302.13563. $C_{15}H_{21}NaNO_4$ requires 302.13628.

(*S*)-4-Isopropyl-2-oxazolidinone 147



$C_6H_{11}NO_2$ 129.16 g.mol^{-1}

L-valinol

L-valinol was prepared by a literature method.[141] L-valine (5 g, 42.68 mmol, 1 eq) was added to a suspension of sodium borohydride (4.03 g, 106.7 mmol, 2.5 eq) in dry THF (115 mL) under nitrogen. The reaction mixture was cooled to 4°C and a solution of iodine (10.83 g, 42.68 mmol, 1 eq) in dry THF (30 mL) was then added dropwise over 1 h. After the gas evolution had ceased, the reaction mixture was heated to reflux for 18 h and then allowed to cool to room temperature. Methanol was added slowly until the mixture became clear and the solution was stirred for 15 min. The organic solvents were removed *in vacuo* and the residue was dissolved in aqueous KOH solution (3M, 100 mL). The mixture was stirred for 3 h and then extracted with dichloromethane (3 x 100 mL). The combined organic extracts were dried (Na_2SO_4), filtered and concentrated *in vacuo* to give L-valinol (3.67 g, 35.57 mmol, 83 %) as a colourless oil which was used without further purification.

^{1}H NMR (300 MHz, $CDCl_3$): δ 0.88 (d, ^3J=6.8 Hz, 3H, CH_3), 0.89 (d, ^3J=6.8 Hz, 3H, CH_3), 1.46-1.60 (m, 1H, C*H*$(CH_3)_2$), 2.05 (br s, 2H), 2.47-2.58 (m, 1H, C*H*NH_2), 3.26 (t, ^3J=^2J=9.9 Hz, 1H, C*H*HOH), 3.61 (dd, ^3J=3.9 Hz, ^2J=10.4 Hz, 1H, CH*H*OH); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 18.3 (CH_3), 19.2 (CH_3), 31.5 (*C*H$(CH_3)_2$), 58.4 (CHN), 64.7 (*C*H_2OH).

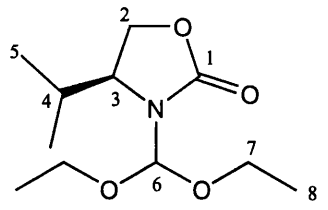
(*S*)-4-Isopropyl-2-oxazolidinone 147

A solution of triphosgene (3.69 g, 12.45 mmol, 0.35 eq) in dry dichloromethane (15 mL) was added dropwise over 1.25 h to a solution of the crude amino alcohol (3.67 g, 35.57 mmol, 1 eq) and triethylamine (10.9 mL, 78.26 mmol, 2.2 eq) in dry dichloromethane (65 mL) under nitrogen at 4°C. The reaction mixture was stirred for a

further 2.5 h at 4 °C and then allowed to warm to room temperature and stirred for 30 min. The reaction was quenched with saturated aqueous NH_4Cl solution (30 mL) and after stirring for 20 min, the mixture was transfered into a separating funnel. The aqueous layer was separated and the organic layer washed with saturated aqueous $NaHCO_3$ solution (30 mL) and brine (30 mL). The combined organic extracts were then dried (Na_2SO_4), filtered and concentrated *in vacuo*. The crude product was twice recrystallised from diethyl ether to give the *title compound* **147** (2.48 g, 19.2 mmol, 45% for the 2 steps) as fine white needles.

Mp 70-71°C (diethyl ether) (lit.,[140] 70-71.5°C (EtOAc/hexane)); R_f (EtOAc) 0.56; $[\alpha]_D^{17}$ +8.6 (*c* 1.0, $CHCl_3$) (lit.,[140] $[\alpha]_D^{25}$ +4.38 (*c* 1.0, $CHCl_3$)); **IR** ($CHCl_3$): ν_{max} 3300 (br, NH), 3018 (m), 2968 (w), 1751 (s, C=O), 1407 (w), 1230 (w) cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$): δ 0.88 (d, ^3J=6.9 Hz, 3H, CH_3), 0.94 (d, ^3J=6.8 Hz, 3H, CH_3), 1.64-1.77 (m, 1H, C*H*(CH_3)$_2$), 3.58 (q, ^3J=^3J=6.7 Hz, CHN), 4.08 (dd, ^3J=6.3 Hz, ^2J=8.7 Hz, 1H, C*H*HO), 4.42 (t, ^3J=^2J=8.7 Hz, 1H, CH*H*O), 6.53 (br s, 1H, NH); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 17.6 (CH_3), 18.0 (CH_3), 32.7 (*C*H(CH_3)$_2$), 58.3 (CHN), 68.6 (CH_2O), 160.2 (C=O); **CI(methane)-MS** *m/z* (%): 130 (MH^+, 100); **HMRS**: MH^+, found 130.08645. $C_6H_{12}NO_2$ requires 130.08626.

(*S*)-3-Diethoxymethyl-4-isopropyl-2-oxazolidinone 148



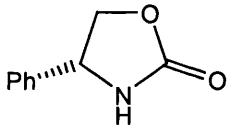
$C_{11}H_{21}NO_4$ 231.29 $g.mol^{-1}$

A mixture of oxazolidinone **147** (120 mg, 0.93 mmol, 1 eq), aluminium chloride (18.6 mg, 0.14 mmol, 0.15 eq) and triethyl orthoformate (4.6 mL, 27.9 mmol, 30 eq) was heated at 155°C for 20 h. The reaction mixture was cooled to room temperature and then quenched with saturated aqueous $NaHCO_3$ solution (5 mL). The aqueous phase was extracted with diethyl ether (10 mL then 5 mL) and the combined organic extracts

were washed with brine (5 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (silica, P.E. 30-40°C/EtOAc 4:1 to 3:1) to give the *title compound* **148** (63 mg, 0.27 mmol, 29%) as a colourless oil.

R_f (P.E. 40-60°C/EtOAc 3:1) 0.38; $[\alpha]_D^{23}$ +26.2 (*c* 1.26, CH_2Cl_2); **IR** (film): ν_{max} 2976 (s), 2945 (m), 2878 (m), 1763 (s, C=O), 1414 (m), 1232 (m), 1063 (s) cm^{-1}; **^{1}H NMR** (400 MHz, DMSO): δ 0.79 (d, $^3J_{5\text{-}4}$=8.6 Hz, 3H, H_5), 0.81 (d, $^3J_{5\text{-}4}$=8.6 Hz, 3H, H_5), 1.12 (t, $^3J_{8\text{-}7}$=7.1 Hz, 3H, H_8), 1.15 (t, $^3J_{8\text{-}7}$=7.1 Hz, 3H, H_8), 2.09-2.18 (m, 1H, H_4), 3.45-3.67 (m, 4H, H_7), 3.90 (ddd, $^3J_{3\text{-}4}$=3.3 Hz, $^3J_{3\text{-}2}$=4.8 Hz, $^3J_{3\text{-}2}$=9.0 Hz, 1H, H_3), 4.12 (dd, $^3J_{2\text{-}3}$=4.8 Hz, ^2J=9.0 Hz, 1H, H_2), 4.24 (t, $^3J_{2\text{-}3}$=^2J=9.0 Hz, 1H, H_2), 5.64 (s, 1H, H_6); **^{13}C NMR** (100 MHz, DMSO): δ 14.1 (C_3), 14.7 (C_8), 17.6 (C_5), 29.0 (C_4), 55.8 (C_3), 61.9 (CH_2), 62.2 (CH_2), 63.1 (CH_2), 102.1 (C_6), 157.0 (C_1); **EI-MS** *m/z* (%): 232 (MH^+, 8), 187 ($[M\text{-}C_2H_5O]^+$, 100), 158 (36), 130 (48), 103 (77); **HMRS**: MH^+, found 232.15519. $C_{11}H_{22}NO_4$ requires 232.15488.

(*R*)-(-)-4-Phenyl-2-oxazolidinone 149



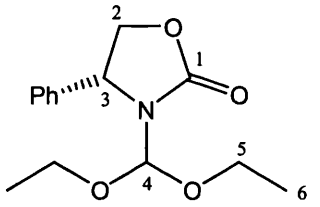
$C_9H_9NO_2$ 163.18 g.mol^{-1}

A solution of triphosgene (0.826 g, 2.78 mmol, 0.35 eq) in dry dichloromethane (5 mL) was added dropwise over 2 h to a solution of (*R*)-(-)-2-phenylglycinol (1.09 g, 7.95 mmol, 1 eq) and triethylamine (2.44 mL, 17.49 mmol, 2.2 eq) in dry dichloromethane (30 mL) under nitrogen at 4°C. The reaction mixture was stirred for a further 30 min at 4 °C and the triethylamine hydrochloride precipitate was then filtered and washed with dry dichloromethane (5 mL). The filtrate was washed with saturated aqueous NH_4Cl solution (15 mL), brine (15 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. As the product was contaminated by triethylamine hydrochloride, the crude product was taken up in EtOAC (60 mL) and the organic layer was washed with saturated aqueous $NaHCO_3$ solution (2 x 20 mL) and brine (20 mL), dried ($MgSO_4$), filtered and

concentrated *in vacuo* to give the *title compound* **149** (0.94 g, 5.76 mmol, 72%) as a white solid.

Mp 129-130°C (lit.,[13] 132-134°C (EtOAc/hexane)); R_f (EtOAc) 0.67; $[\alpha]_D^{17}$ -60.4 (*c* 1.0, $CHCl_3$) (lit.,[13] $[\alpha]_D^{20}$ -57.7 (*c* 1.083, $CHCl_3$)); **IR** ($CHCl_3$): ν_{max} 3268 (br, NH), 2915 (w), 1757 (s, C=O), 1399 (w), 1216 (m), 1042 (w), 925 (w), 757 (s) cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$): δ 4.15 (dd, ^3J=6.9 Hz, ^2J=8.6 Hz, 1H, C*H*HO), 4.69 (t, ^3J=^2J=8.6 Hz, 1H, CH*H*O), 4.93 (dd, ^3J=6.9 Hz, ^3J=8.6 Hz, 1H, CHN), 6.32 (br s, 1H, NH), 7.227-7.41 (m, $5H_{arom}$); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 56.3 (CHN), 72.5 (CH_2O), 126.0 (CH), 128.7 (CH), 129.1 (CH), 139.5 (C_q), 159.9 (C=O); **EI-MS** *m/z* (%): 163 (M^+, 24), 133 (73), 104 (100), 91 (30), 77 (Ph^+, 32).

(*R*)-(-)-3-Diethoxymethyl-4-phenyl-2-oxazolidinone 150



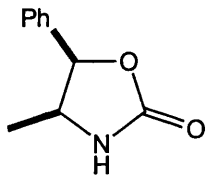
$C_{14}H_{19}NO_4$ 265.31 $g.mol^{-1}$

A mixture of oxazolidinone **149** (0.87 g, 5.33 mmol, 1 eq), aluminium chloride (0.107 g, 0.80 mmol, 0.15 eq) and triethyl orthoformate (26.3 mL, 0.16 mol, 30 eq) was heated at 140°C for 16 h. The reaction mixture was cooled to room temperature and then quenched with saturated aqueous $NaHCO_3$ solution (25 mL). The aqueous phase was extracted with diethyl ether (2 x50 mL) and the combined organic extracts were washed with brine (25 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (silica, P.E. 30-40°C/EtOAc 7:3) to give the *title compound* **150** (0.464 g, 1.75 mmol, 33%) as a colourless oil.

R_f (P.E. 40-60°C/EtOAc 7:3) 0.47; $[\alpha]_D^{17}$ -49.9 (*c* 1.8, CH_2Cl_2); **IR** (film): ν_{max} 2978 (m), 2903 (w), 1761 (s, C=O), 1458 (m), 1402 (m), 1216 (m), 1066 (s), 765 (w), 707

(m) cm^{-1}; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 0.65 (t, $^3J_{6\text{-}5}$=7.1 Hz, 3H, H_6), 1.21 (t, $^3J_{6\text{-}5}$=7.1 Hz, 3H, H_7), 3.10 (qd, $^3J_{5\text{-}6}$=7.1 Hz, ^2J=9.1 Hz, 1H, H_5), 3.32 (qd, $^3J_{5\text{-}6}$=7.1 Hz, ^2J=9.3 Hz, 1H, H_5), 3.66 (qd, $^3J_{5\text{-}6}$=7.1 Hz, ^2J=9.4 Hz, 1H, H_5), 4.19 (qd, $^3J_{5\text{-}6}$=7.1 Hz, ^2J=9.4 Hz, 1H, H_5), 4.19 (dd, $^3J_{2\text{-}3}$=5.9 Hz, ^2J=8.7 Hz, 1H, H_2), 4.60 (t, $^3J_{2\text{-}3}$=^2J=8.8 Hz, 1H, H_2), 5.00 (dd, $^3J_{3\text{-}2}$=5.9 Hz, $^3J_{3\text{-}2}$=9.0 Hz, 1H, H_3), 5.71 (s, 1H, H_4), 7.24-7.36 (m, 5H, H_{arom}); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 13.8 (C_6), 14.7 (C_6), 55.4 (C_3), 61.8 (C_5), 62.8 (C_5), 70.9 (C_2), 102.5 (C_4), 126.9 (CH), 128.2 (CH), 128.5 (CH), 140.1 (C_q), 157.9 (C_1); **EI-MS** *m/z* (%): 265 (M^+, 14), 220 ([M-C_2H_5O]$^+$, 86), 192 (77), 148 (62), 121 (71), 103 (100), 91 (38), 77 (Ph^+, 53), 75 (92); **HMRS**: M^+, found 265.12982. $C_{14}H_{19}NO_4$ requires 265.13086.

4-Methyl-5-phenyl-2-oxazolidinone 151



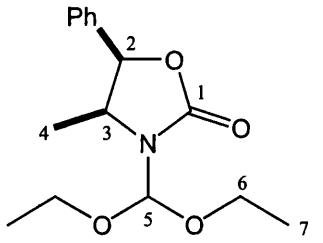
$C_{10}H_{11}NO_2$ 177.20 g.mol^{-1}

A solution of triphosgene (1.22 g, 4.1 mmol, 0.35 eq) in dry dichloromethane (5 mL) was added dropwise over 1 h to a suspension of norephedrine hydrochloride (2.2 g, 11.72 mmol, 1 eq) and triethylamine (5.23 mL, 37.51 mmol, 3.2 eq) in dry dichloromethane (40 mL) under nitrogen at 4°C. The reaction mixture was stirred for a further 30 min at 4 °C and the triethylamine hydrochloride precipitate filtered and washed with dichloromethane (2 x 20 mL). The filtrate was washed with saturated aqueous NH_4Cl solution (20 mL), saturated aqueous $NaHCO_3$ solution (20 mL) and brine (20 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to give the *title compound* **151** (1.52 g, 8.56 mmol, 73%) as a white solid.

Mp 146-148°C (lit.,[142] 146-146.5°C); R_f (EtOAc) 0.54; **IR** ($CDCl_3$): ν_{max} 3261 (br, NH), 2998 (w), 1747 (s, C=O), 1724 (s), 1379 (m), 1230 (m), 908 (s), 732 (s) cm^{-1}; **^{1}H NMR** (500 MHz, $CDCl_3$): δ0.79 (d, ^3J=6.5 Hz, 3H, CH_3), 4.19 (qd, ^3J=6.5 Hz, ^3J=8.0 Hz, 1H, CHN), 5.70 (d, ^3J=8.0 Hz, 1H, CHO), 5.68 (br s, 1H, NH), 7.25-7.39 (m, 5H, H_{arom});

^{13}C NMR (75 MHz, $CDCl_3$): δ 17.5 (CH_3), 52.4 (CHN), 81.0 (CH_2O), 125.9 (CH), 128.5 (CH), 134.8 (C_q), 159.4 (C=O).

3-Diethoxymethyl-4-methyl-5-phenyl-2-oxazolidinone 152

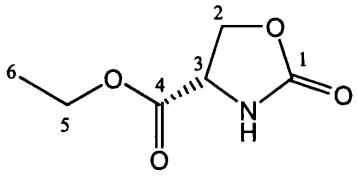


$C_{15}H_{21}NO_4$ 279.34 g.mol^{-1}

A mixture of oxazolidinone **151** (1.3 g, 7.34 mmol, 1 eq), aluminium chloride (0.147 g, 1.1 mmol, 0.15 eq) and triethyl orthoformate (36.2 mL, 0.22 mol, 30 eq) was heated at 150°C for 16 h. The reaction mixture was cooled to room temperature and then quenched with saturated aqueous $NaHCO_3$ solution (35 mL). The aqueous phase was extracted with diethyl ether (70 mL then 35 mL) and the combined organic extracts were washed with brine (35 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (silica, P.E. 30-40°C/EtOAc 8.5:1.5to 4:1) to give the *title compound* **152** (0.77 g, 2.76 mmol, 38%) as a yellow oil.

R_f (P.E. 30-40°C/EtOAc 4:1) 0.3; **IR** (film): ν_{max} 2978 (m), 2935 (w), 1759 (s, C=O), 1410 (m), 1236 (m), 1064 (s), 747 (m), 702 (m) cm^{-1}; **^{1}H NMR** (500 MHz, $CDCl_3$): δ0.86 (d, $^3J_{4\text{-}3}$=6.5 Hz, 3H, H_4), 1.19 (t, $^3J_{7\text{-}6}$=7.0 Hz, 3H, H_7), 1.23 (t, $^3J_{7\text{-}6}$=7.0 Hz, 3H, H_7), 3.53-3.75 (m, 4H, H_6), 4.32 (qd, $^3J_{3\text{-}4}$=6.5 Hz, $^3J_{3\text{-}2}$=8.1 Hz, 1H, H_3), 5.56 (d, $^3J_{2\text{-}3}$=8.1 Hz, 1H, H_2), 5.82 (s, 1H, H_5), 7.22-7.39 (m, 5H, H_{arom}); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 14.7 (C_7), 14.8 (C_7), 16.4 (C_4), 52.1 (C_3), 62.4 (C_6), 63.0 (C_6), 79.7 (C_2), 102.3 (C_5), 126.0 (CH), 128.4 (CH), 134.8 (C_q), 157.1 (C_1); **CI(ammonia)-MS** *m/z* (%): 279 (M^+, 15), 249 (76), 175 (100), 160 (80); **HMRS**: M^+, found 279.14751. $C_{15}H_{21}NO_4$ requires 279.14705.

(*S*)-Ethyl-2-oxazolidinone-4-carboxylate 154

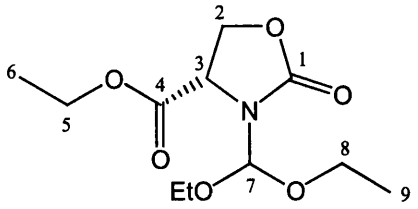


$C_6H_9NO_4$ 159.14 g.mol^{-1}

A solution of triphosgene (3.67 g, 12.38 mmol, 0.35 eq) in dry dichloromethane (20 mL) was added dropwise over 1.25 h to a suspension of L-serine ethyl ester hydrochloride (6.0 g, 35.37 mmol, 1 eq) and triethylamine (15.78 mL, 113.2 mmol, 3.2 eq) in dry dichloromethane (120 mL) under nitrogen at 4°C. The reaction mixture was stirred for a further 2.25 h at 4 °C and then allowed to warm to room temperature and stirred for 30 min. Saturated aqueous NH_4Cl solution (30 mL) and dichloromethane (40 mL) were added to the reaction mixture and after stirring for 10 min, the mixture was transfered into a separating funnel. The aqueous layer was separated and the organic layer washed with saturated aqueous $NaHCO_3$ solution (30 mL) and brine (30 mL). The combined organic extracts were then dried ($MgSO_4$), filtered and concentrated *in vacuo* to give the *title compound* **154** contaminated by traces of triethylamine hydrochloride (4.47 g, 28.1 mmol, 79%) as a white solid.

Mp 69-71°C (EtOAc/hexane); R_f (P.E. 40-60°C/EtOAc 1:1) 0.15; $[\alpha]_D^{22}$-24.0 (*c* 1.0, CH_2Cl_2); **IR** ($CHCl_3$): ν_{max} 3270 (br, NH), 1745 (s, C=O), 1402 (m), 1379 (m), 1214 (s), 1131 (m), 1019 (m), 932 (w), 769 (w) cm^{-1}; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 1.30 (t, $^3J_{6\text{-}5}$=7.2 Hz, 3H, H_6), 4.26 (q, $^3J_{5\text{-}6}$=7.2 Hz, 2H, H_5), 4.37 (dd, $^3J_{2\text{-}3}$=4.6 Hz, ^2J=9.6 Hz, 1H, H_2), 4.52 (dd, $^3J_{3\text{-}2}$=4.6 Hz, $^3J_{3\text{-}2}$=9.0 Hz, H_3), 4.60 (dd, $^3J_{2\text{-}3}$=9.0 Hz, ^2J=9.6 Hz, 1H, H_2), 5.58 (br s, 1H, NH); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 13.9 (C_6), 53.7 (C_3), 62.2 (CH_2), 66.6 (CH_2), 159.1 (C_1), 170.1 (C_4); **FAB-MS** *m/z* (%): 160 (MH^+, 100); **HMRS**: MH^+, found 160.06086. $C_6H_{10}NO_4$ requires 160.06098.

(*S*)-Ethyl-3-diethoxymethyl-2-oxazolidinone-4-carboxylate 155

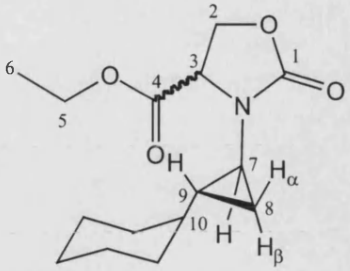


$C_{11}H_{19}NO_6$ 261.27 g.mol^{-1}

A mixture of oxazolidinone **154** (1.5 g, 9.42 mmol, 1 eq), aluminium chloride (0.19 g, 1.41 mmol, 0.15 eq) and triethyl orthoformate (46 mL, 0.28 mol, 30 eq) was heated at 160°C for 18 h. The reaction mixture was cooled to room temperature and then quenched with saturated aqueous $NaHCO_3$ solution (40 mL). The aqueous phase was extracted with diethyl ether (2 x 40 mL) and the combined organic extracts were washed with brine (40 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (silica, P.E. 30-40°C/EtOAc 3:1 to 7:3) to give the *title compound* **155** (1.35 g, 5.17 mmol, 55%) as a yellow oil.

***R*$_f$** (P.E. 40-60°C/EtOAc 7:3) 0.29; $[\alpha]_D^{20}$ -22.4 (*c* 1.02, CH_2Cl_2); **IR** (film): ν_{max} 2981 (m), 2955 (w), 2905 (w), 1770 (s, C=O), 1751 (s, C=O), 1405 (m), 1375 (m), 1066 (s), 1025 (m) cm^{-1}; **^{1}H NMR** (500 MHz, DMSO): δ 1.05 (t, $^3J_{9\text{-}8}$=7.0 Hz, 3H, H_9), 1.13 (t, $^3J_{9\text{-}8}$=7.0 Hz, 3H, H_9), 1.21 (t, $^3J_{6\text{-}5}$=7.0 Hz, 3H, H_6), 3.45-3.59 (m, 4H, H_8), 4.07-4.17 (m, 2H, H_5), 4.20 (dd, $^3J_{2\text{-}3}$=3.7 Hz, ^2J=9.0 Hz, 1H, H_2), 4.42 (dd, $^3J_{3\text{-}2}$=3.7 Hz, $^3J_{3\text{-}2}$=9.1 Hz, H_3), 4.53 (t, $^3J_{2\text{-}3}$=^2J=9.0 Hz, 1H, H_2), 5.65 (s, 1H, H_7); **^{13}C NMR** (125 MHz, DMSO): δ 13.8 (C_6), 14.4 (C_9), 14.7 (C_9), 52.7 (C_3), 61.1 (C_8), 61.1 (C_5), 62.2 (C_8), 65.8 (C_2), 100.8 (C_7), 156.1 (C_1), 170.6 (C_4); **EI-MS** *m/z* (%): 261 (M^+, 49), 216 ([M-C_2H_5O]$^+$, 90), 188 (100), 160 (95); **HMRS**: M^+, found 261.12092. $C_{11}H_{19}NO_6$ requires 261.12069.

Ethyl-3-(2-cyclohexylcyclopropyl)-2-oxazolidinone-4-carboxylate 156 and 157

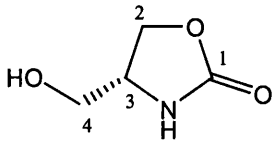


$C_{15}H_{23}NO_4$ 281.35 g.mol^{-1}

A solution of *N*-diethoxymethyl-2-oxazolidinone **155** (0.74 g, 2.83 mmol, 1.25 eq) in dry diethyl ether (3.5 mL) was added *via* a motorised syringe pump over 6 h to a vigorously stirred mixture of zinc amalgam (1.85 g, 28.3 mmol, 12.5 eq), zinc chloride (1M solution in diethyl ether, 2.83 mL, 2.83 mmol, 1.25 eq), chlorotrimethylsilane (1.79 mL, 14.12 mmol, 6.25 eq) and vinylcyclohexane (0.25 g, 2.26 mmol, 1 eq) in dry diethyl ether (11.75 mL) under nitrogen at reflux. The mixture was stirred for 10 h and then allowed to cool to room temperature. The reaction was quenched with saturated aqueous $NaHCO_3$ solution (15 mL) and after stirring for 20 min, the mixture was filtered through celite and the separated zinc washed with dichloromethane (20 mL). The organic solvents were removed *in vacuo* and the aqueous layer was extracted with dichloromethane (2 x 20 mL). The combined organic extracts were washed with brine (20 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (silica, P.E. 30-40°C/EtOAc 3:1 to 6.5:3.5) to give an inseparable mixture of cyclopropanes **156** and **157** contaminated by 10 wt. % of ethyl-*N*-formyl-2-oxazolidinone-4-carboxylate (0.34 g, 1.09 mmol of **156** and **157** after correction, 48% of **156** and **157** after correction) as a yellow oil.

Mixture of *trans* A and B isomers: **^{1}H NMR** (400 MHz, $CDCl_3$): δ 0.47-0.79 (m, 6H), 0.79-0.92 (m, 12H), 1.27 (t, $^3J_{6\text{-}5}$=7.2 Hz, 3H, H_{6B}), 1.28 (t, $^3J_{6\text{-}5}$=7.1 Hz, 3H, H_{6A}), 1.55-1.72 (m, 10H), 2.37 (td, $^3J_{7\text{-}8\alpha}$=$^3J_{7\text{-}9}$=3.4 Hz, $^3J_{7\text{-}8\beta}$=7.2 Hz, 1H, H_{7B}), 2.42 (td, $^3J_{7\text{-}8\alpha}$=$^3J_{7\text{-}9}$=3.4 Hz, $^3J_{7\text{-}8\beta}$=7.0 Hz, 1H, H_{7A}), 4.14-4.36 (m, 10H).

(*R*)-4-Hydroxymethyl-2-oxazolidinone 158

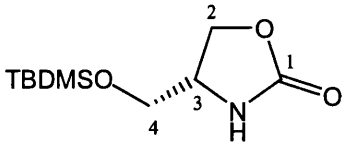


$C_4H_7NO_3$ 117.10 g.mol^{-1}

Sodium borohydride (0.45 g, 11.74 mmol, 1.05 eq) was added portionwise to a solution of (*S*)-ethyl-2-oxazolidinone-4-carboxylate **154** (1.78 g, 11.18 mmol, 1 eq) in absolute ethanol (22 mL) under nitrogen at 4°C. The reaction mixture was stirred for a further 10 min at 4 °C and then allowed to warm to room temperature and stirred for 2 h. The reaction was quenched carefully with saturated aqueous NH_4Cl solution (1.8 mL) and after stirring for 30 min the mixture was filtered through celite. The solvents were removed *in vacuo* and the crude product was purified by flash column chromatography (silica, EtOAc/MeOH 9:1 to 8.5:1.5) to give the *alcohol* **158** (0.99 g, 8.45 mmol, 76%,) as a yellowish solid.

Mp 96-99°C (lit.,[109] 96-99°C (MeOH)); R_f (EtOAc/MeOH 9:1) 0.27; $[\alpha]_D^{20}$ +25.7 (*c* 1.24, MeOH) (lit.,[109] $[\alpha]_D^{25}$ +32.25 (*c* 1.044, MeOH)); **IR** ($CHCl_3$): ν_{max} 3330 (br, NH), 2927 (w), 2880 (w), 1735 (s, C=O), 1418 (m), 1258 (m), 1094 (w), 1038 (m), 939 (w), 771 (w), 711 (w) cm^{-1}; **^{1}H NMR** (300 MHz, DMSO): δ 3.36 (t, $^3J_{4\text{-}3}=^3J_{4\text{-}OH}$=4.9 Hz, 2H, H_4), 3.75 (qd, $^3J_{3\text{-}2}=^3J_{3\text{-}4}$=4.9 Hz, $^3J_{3\text{-}2}$=8.5 Hz, 1H, H_3), 4.05 (dd, $^3J_{2\text{-}3}$=4.9 Hz, ^2J=8.5 Hz, 1H, H_2), 4.30 (t, $^3J_{2\text{-}3}=^2J$=8.5 Hz, H_2), 4.92 (t, $^3J_{OH\text{-}4}$=4.9 Hz, 1H, OH), 7.54 (br s, 1H, NH); **^{13}C NMR** (125 MHz, DMSO): δ 53.1 (C_3), 62.7 (C_4), 66.3 (C_2), 159.0 (C_1); **EI-MS** *m/z* (%): 118 (MH^+, 7), 86 ($[M\text{-}CH_2OH]^+$, 100); **HMRS**: MH^+, found 118.04966. $C_4H_8NO_3$ requires 118.04987.

(*S*)-4-[[(*tert*-Butyldimethylsilyl)oxy]methyl]-2-oxazolidinone 159

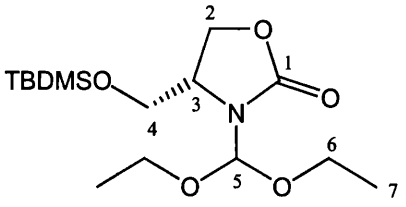


$C_{10}H_{21}NO_3Si$ 231.37 g.mol^{-1}

Tert-butyldimethylsilyl chloride (1.23 g, 8.17 mmol, 1.1 eq) and imidazole (1.11 g, 16.35 mmol, 2.2 eq) were added successively to a solution of alcohol **158** (0.87 g, 7.43 mmol, 1 eq) in dry DMF (10 mL) under nitrogen at 4°C. The reaction mixture was stirred for a further 30 min at 4 °C and then allowed to warm to room temperature and stirred for 44 h. The reaction was quenched with saturated aqueous $NaHCO_3$ solution (40 mL) and the aqueous layer was extracted with EtOAc (3 x 40 mL). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (silica, P.E. 40-60°C/EtOAc 1:1) to give the *title compound* **159** (1.39 g, 6.01 mmol, 81%,) as a white solid.

Mp 76-79°C (lit.,[143] 59-60°C); R_f (P.E. 40-60°C/EtOAc 1:1) 0.28; $[\alpha]_D^{19}$ +34.6 (*c* 1.44, $CHCl_3$) (lit.,[143] $[\alpha]_D^{21}$ +13.4 (*c* 1.45, $CHCl_3$)); **IR** ($CDCl_3$): ν_{max} 3300 (br, NH), 2926 (w), 2864 (w), 1751 (s, C=O), 1414 (w), 1252 (w), 1136 (w), 1043 (m), 941 (w), 839 (m), 779 (m) cm^{-1}; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 0.04 (s, 6H, 2 x CH_3Si), 0.86 (s, 9H, $C(CH_3)_3$), 3.59 (d, $^3J_{4\text{-}3}$=5.5 Hz, 2H, H_4), 3.87-3.93 (m, 1H, H_3), 4.14 (dd, $^3J_{2\text{-}3}$=4.9 Hz, ^2J=8.8 Hz, 1H, H_2), 4.42 (t, $^3J_{2\text{-}3}$=^2J=8.7 Hz, 1H, H_2), 5.69 (br s, 1H, NH); **^{13}C NMR** (125 MHz, $CDCl_3$): δ -5.5 (CH_3Si), 18.1 ($C(CH_3)_3$), 25.7 ($C(CH_3)_3$), 53.6 (C_3), 64.8 (CH_2), 67.0 (CH_2), 73.4 (CH_2), 159.6 (C_1); **EI-MS** *m/z* (%): 232 (MH^+, 15), 216 ($[M\text{-}CH_3]^+$, 62), 174 ($[M\text{-}C_4H_9]^+$, 82), 131 (100), 101 ($[M+H\text{-}OTBDMS]^+$, 93), 75 (92); **HMRS**: MH^+, found 232.13671. $C_{10}H_{22}NO_3Si$ requires 232.13635; **Anal.** found: C, 51.94; H, 9.47; N, 6.03. Calcd for $C_{10}H_{21}NO_3Si$: C, 51.91; H, 9.15; N, 6.05.

(*S*)-3-Diethoxymethyl-4-[[(*tert*-butyldimethylsilyl)oxy]methyl]-2-oxazolidinone 160

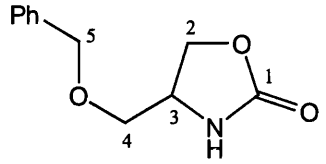


$C_{16}H_{23}NO_5$ 333.50 g.mol^{-1}

A mixture of oxazolidinone **159** (1.2 g, 5.19 mmol, 1 eq), aluminium chloride (0.104 g, 0.78 mmol, 0.15 eq) and triethyl orthoformate (25.6 mL, 0.16 mol, 30 eq) was heated at 155°C for 18 h. The reaction mixture was cooled to room temperature and the solvent removed *in vacuo*. The residue was partitioned between EtOAc (60 mL) and saturated aqueous $NaHCO_3$ solution (20 mL). The organic layer was separated and the aqueous phase was extracted with EtOAc (30 mL). The combined organic extracts were washed with brine (20 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (silica, P.E. 40-60°C/EtOAc 4:1 to 3:1) to give the *title compound* **160** (1.04 g, 3.11 mmol, 60%) as a colourless oil. However, the instability of **160** precluded complete characterisation.

R_f (P.E. 40-60°C/EtOAc 75:35) 0.31; **IR** (film): ν_{max} 2977 (m), 2954 (m), 2929 (m), 2858 (m), 1758 (s, C=O), 1408 (m), 1250 (m), 1099 (s), 1065 (s), 854 (m, Si-C), 837 (m, Si-C), 773 (m) cm^{-1}; **^{1}H NMR** (400 MHz, DMSO): δ 0.02 (s, 3H, CH_3Si), 0.04 (s, 3H, CH_3Si), 0.84 (s, 9H, $C(CH_3)_3$), 1.12 (t, $^3J_{7\text{-}6}$=7.3 Hz, 3H, H_7), 1.13 (t, $^3J_{7\text{-}6}$=7.3 Hz, 3H, H_7), 3.46-3.60 (m, 4H, H_6), 3.67 (dd, $^3J_{4\text{-}3}$=2.9 Hz, ^2J=10.4 Hz, 1H, H_4), 3.71 (dd, $^3J_{4\text{-}3}$=4.5 Hz, ^2J=10.4 Hz, 1H, H_4), 3.98 (dtd, $^3J_{3\text{-}4}$=2.9 Hz, $^3J_{3\text{-}4}$=$^3J_{3\text{-}2}$=4.5 Hz, $^3J_{3\text{-}2}$=8.5 Hz, 1H, H_3), 4.11 (dd, $^3J_{2\text{-}3}$=4.5 Hz, ^2J=8.5 Hz, 1H, H_2), 4.35 (t, $^3J_{2\text{-}3}$=^2J=8.5 Hz, 1H, H_2), 5.64 (s, 1H, H_5); **^{13}C NMR** (100 MHz, , DMSO): δ -5.6(CH_3Si), -5.5 (CH_3Si), 14.7 (2 x C_7), 17.8 ($C(CH_3)_3$), 25.6 ($C(CH_3)_3$), 52.3 (C_3), 61.6 (CH_2), 61.8 (CH_2), 62.8 (CH_2), 65.5 (CH_2), 101.6 (C_5), 156.9 (C_1).

4-Benzyloxymethyl-2-oxazolidinone 162



$C_{11}H_{13}NO_3$ 207.23 g.mol^{-1}

***O*-benzyl-DL-serinol**

O-benzyl-DL-serinol was prepared by a modification of the literature method.[141] *O*-benzyl-DL-serine (2.5 g, 12.81 mmol, 1 eq) was added to a suspension of sodium borohydride (1.21 g, 32.01 mmol, 2.5 eq) in dry THF (35 mL) under nitrogen. The reaction mixture was cooled to 4°C and a solution of iodine (3.25 g, 12.81 mmol, 1 eq) in dry THF (7.5 mL) was then added dropwise over 45 min. After the gas evolution had ceased, the reaction mixture was heated to reflux for 16 h and then allowed to cool to room temperature. Methanol was added slowly until the mixture became clear and the solution was stirred for 20 min. The organic solvents were removed *in vacuo* and the residue was dissolved in aqueous KOH solution (20 %, 25 mL). The mixture was stirred for 4 h and water (25 mL) and dichloromethane (50 mL) were added. The mixture was transfered into a separating funnel and the organic layer was separated. The aqueous layer was extracted with dichloromethane (2 x 50 mL). The combined organic extracts were dried (Na_2SO_4), filtered and concentrated *in vacuo* to give *O*-benzyl-DL-serinol (2.13 g, 11.75 mmol, 92 %) as a greyish solid which was used without further purification.

^{1}H NMR (300 MHz, $CDCl_3$): δ 2.09 (br s, 3H, OH and NH_2), 3.12 (br s, 1H, C*H*NH_2), 3.40-3.68 (m, 4H, 2 x CH_2), 4.52 (s, 2H, OCH_2Ph), 7.25-7.42 (m, 5H, H_{arom}); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 52.3 (CHN), 64.4 (CH_2OH), 72.9 ($CHCH_2O$), 73.4 (OCH_2Ph), 127.7 (CH), 127.8 (CH), 128.5 (CH), 138.0 (C_q).

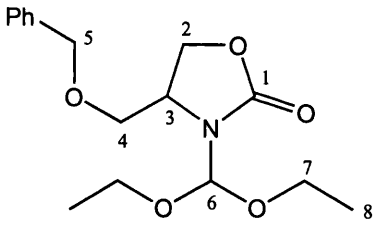
4-Benzyloxymethyl-2-oxazolidinone 162

A solution of triphosgene (1.22 g, 4.11 mmol, 0.35 eq) in dry dichloromethane (4 mL) was added dropwise over 1 h to a suspension of crude *O*-benzyl-DL-serinol (2.13 g,

11.75 mmol, 1 eq) and triethylamine (3.6 mL, 25.85 mmol, 2.2 eq) in dry dichloromethane (50 mL) under nitrogen at 4°C. The mixture was stirred for a further h at 4 °C and then allowed to warm to room temperature and stirred for 1 h. The reaction was quenched with saturated aqueous NH_4Cl solution (20 mL) and after stirring for 20 min, the mixture was transfered into a separating funnel. The aqueous layer was separated and the organic layer washed with water (20 mL). The combined aqueous layers were extracted with EtOAc (2 x 40 mL) and the combined organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (silica, P.E. 40-60°C/EtOAc 3:2 to 7:3) to give the *title compound* **162** (1.48 g, 7.14 mmol, 56%) as a yellow oil.

R_f (EtOAc/P.E. 40-60°C 7:3) 0.3; **IR** ($CDCl_3$): ν_{max} 3320 (br, NH), 2906 (w), 2864 (w), 1752 (s, C=O), 1410 (m), 1232 (m), 1096 (s), 1056 (s), 1036 (s), 742 (w), 700 (w) cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 3.43 (d, $^3J_{4\text{-}3}$=5.7 Hz, 2H, H_4), 3.93-4.02 (m, 1H, H_3), 4.11 (dd, $^3J_{2\text{-}3}$=5.1 Hz, ^2J=8.7 Hz, 1H, H_2), 4.39 (t, $^3J_{2\text{-}3}$=^2J=8.7 Hz, 1H, H_2), 4.50 (s, 2H, H_5), 6.46 (br s, 1H, NH), 7.24-7.35 (m, 5H, H_{arom}); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 51.8 (C_3), 62.2 (CH_2), 71.4 (CH_2), 73.4 (CH_2), 127.6 (CH), 127.8 127.6 (CH), 137.3 (C_q), 159.9 (C_1); **EI-MS** *m/z* (%): 208 (MH^+, 4), 146 (100); **HMRS**: MH^+, found 208.09751. $C_{11}H_{14}NO_3$ requires 208.09682.

4-Benzyloxymethyl-3-diethoxymethyl-2-oxazolidinone 163



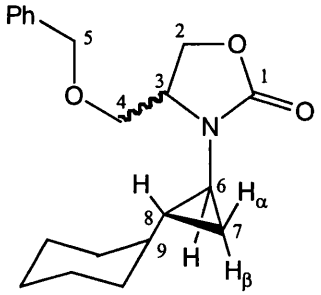
$C_{16}H_{23}NO_5$ 309.36 g.mol^{-1}

A mixture of oxazolidinone **162** (1.31 g, 6.32 mmol, 1 eq), aluminium chloride (0.126 g, 0.95 mmol, 0.15 eq) and triethyl orthoformate (31 mL, 0.19 mol, 30 eq) was heated at 155°C for 20 h. The reaction mixture was cooled to room temperature and the solvent removed *in vacuo*. The residue was partitioned between EtOAc (60 mL) and saturated aqueous $NaHCO_3$ solution (20 mL). The organic layer was separated and the aqueous

phase was then extracted with EtOAc (20 mL). The combined organic extracts were washed with brine (20 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (silica, P.E. 40-60°C/EtOAc 4:1 to 7:3) to give the *title compound* **163** (1.42 g, 4.59 mmol, 73%) as a colourless oil.

R_f (P.E. 30-40°C/EtOAc 7:3) 0.31; **IR** (film): ν_{max} 2978 (m), 1759 (s, C=O), 1414 (m), 1242 (m), 1220 (m), 1063 (s), 739 (m), 700 (m) cm^{-1}; **^{1}H NMR** (400 MHz, DMSO): δ 1.07 (t, $^3J_{8\text{-}7}$=7.0 Hz, 3H, H_8), 1.13 (t, $^3J_{8\text{-}7}$=7.0 Hz, 3H, H_8), 3.43-3.57 (m, 4H, H_7), 3.58 (d, $^3J_{4\text{-}3}$=4.2 Hz, 2H, H_4), 4.08 (qd, $^3J_{3\text{-}2}$=$^3J_{3\text{-}4}$=4.6 Hz, $^3J_{3\text{-}2}$=8.7 Hz, 1H, H_3), 4.19 (dd, $^3J_{2\text{-}3}$=4.8 Hz, ^2J=8.5 Hz, 1H, H_2), 4.38 (t, $^3J_{2\text{-}3}$=^2J=8.7 Hz, 1H, H_2), 4.47 (d, ^2J=12.1 Hz, 1H, H_5), 4.51 (d, ^2J=12.1 Hz, 1H, H_5), 5.64 (s, 1H, H_6), 7.25-7.37 (m, 5H, H_{arom}); **^{13}C NMR** (100 MHz, DMSO): δ 14.6 (C_8), 14.7 (C_8), 50.8 (C_3), 61.7 (CH_2), 62.0 (CH_2), 65.8 (CH_2), 69.6 (CH_2), 72.5 (CH_2), 101.6 (C_6), 127.6 (CH), 128.3 (CH), 138.1 (C_q), 156.9 (C_1); **EI-MS** *m/z* (%): 309 (M^+, 6), 280 ($[M\text{-}C_2H_5]^+$, 42), 264 ($[M\text{-}C_2H_5O]^+$, 59), 190 (32), 157 (51), 128 (52), 103 (100), 91 (Bn^+, 98), 77 (Ph^+, 30); **HMRS**: M^+, found 309.15778. $C_{16}H_{23}NO_5$ requires 309.15707.

4-Benzyloxymethyl –3-(2-cyclohexylcyclopropyl)-2oxazolidinone 166 and 167



$C_{20}H_{27}NO_3$ 329.44 $g.mol^{-1}$

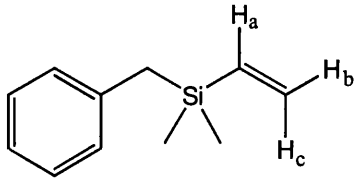
A solution of *N*-diethoxymethyl-2-oxazolidinone **163** (0.387 g, 1.25 mmol, 1.25 eq) in dry diethyl ether (1.25 mL) was added *via* a motorised syringe pump over 6 h to a vigorously stirred mixture of zinc amalgam (0.82 g, 12.5 mmol, 12.5 eq), zinc chloride (1M solution in diethyl ether, 1.25 mL, 1.25 mmol, 1.25 eq), chlorotrimethylsilane (0.79 mL, 6.25 mmol, 6.25 eq) and vinylcyclohexane (0.11 g, 1.0 mmol, 1 eq) in dry diethyl ether (5.5 mL) under nitrogen at reflux. The mixture was stirred for 18 h and then

allowed to cool to room temperature. The reaction was quenched with saturated aqueous $NaHCO_3$ solution (15 mL) and after stirring for 20 min, the mixture was filtered through celite and the separated zinc washed with diethyl ether (20 mL). The organic solvents were removed *in vacuo* and the aqueous layer was extracted with diethyl ether (3 x 15 mL). The combined organic extracts were washed with brine (15 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (silica, P.E. 30-40°C/EtOAc 4:1 to 7:3) to give a mixture of cyclopropanes **166** and **167** contaminated by 10 wt. % of 4-benzyloxymethyl-*N*-formyl-2-oxazolidinone (0.168 g, 0.46 mmol of **166** and **167** after correction, 46% of **166** and **167** after correction) as a yellow oil.

Isomer A: **^{1}H NMR** (500 MHz, $CDCl_3$): δ 0.45-0.56 (m, 1H, H_9), 0.64-0.74 (m, 2H), 0.90-1.17 (m, 5H), 1.54-1.70 (m, 6H), 2.09 (td, $^3J_{6\text{-}7\alpha}=^3J_{6\text{-}8}=3.7$ Hz, $^3J_{6\text{-}7\beta}=6.9$ Hz, 1H, H_6), 3.54 (dd, $^3J_{4\text{-}3}=3.4$ Hz, $^2J=9.5$ Hz, 1H, H_4), 3.59 (dd, $^3J_{4\text{-}3}=5.7$ Hz, $^2J=9.5$ Hz, 1H, H_4), 3.65-3.70 (m, 1H, H_3), 4.16 (dd, $^3J_{2\text{-}3}=4.3$ Hz, $^2J=8.7$ Hz, 1H, H_2), 4.19 (t, $^3J_{2\text{-}3}=^2J=8.7$ Hz, 1H, H_2), 4.52 (d, $^2J=12.1$ Hz, 1H, H_5), 4.56 (d, $^2J=12.1$ Hz, 1H, H_5), 7.23-7.35 (m, 5H, H_{arom}); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 13.6 (C_7), 25.5 (C_8), 26.0 (2 x CH_2), 26.2 (CH_2), 28.9 (C_6), 32.2 (CH_2), 32.7 (CH_2), 40.5 (C_9), 56.2 (C_3), 65.0 (C_2), 67.0 (C_4), 73.4 (C_5), 127.8 (CH), 128.0 (CH), 128.5 (CH), 137.3 (C_q), 158.0 (C_1).

Isomer B: **^{1}H NMR** (500 MHz, $CDCl_3$): δ 0.48 (ddd, $^2J_{7\beta\text{-}7\alpha}=5.4$ Hz, $^3J_{7\beta\text{-}8}=6.4$ Hz, $^3J_{7\beta\text{-}6}=7.2$ Hz, 1H, $H_{7\beta}$), 0.56-0.63 (m, 1H, H_9), 0.65 (ddd, $^3J_{7\alpha\text{-}6}=3.5$ Hz, $^2J_{7\alpha\text{-}7\beta}=5.4$ Hz, $^3J_{7\alpha\text{-}8}=9.2$ Hz, 1H, $H_{7\alpha}$), 0.91-1.20 (m, 6H), 1.55-1.75 (m, 4H), 1.90-1.98 (m, 1H), 2.07 (td, $^3J_{6\text{-}7\alpha}=^3J_{6\text{-}8}=3.5$ Hz, $^3J_{6\text{-}7\beta}=7.2$ Hz, 1H, H_6), 3.55 (dd, $^3J_{4\text{-}3}=4.1$ Hz, $^2J=9.7$ Hz, 1H, H_4), 3.57 (dd, $^3J_{4\text{-}3}=5.3$ Hz, $^2J=9.7$ Hz, 1H, H_4), 3.67-3.73 (m, 1H, H_3), 4.13 (dd, $^3J_{2\text{-}3}=4.5$ Hz, $^2J=8.7$ Hz, 1H, H_2), 4.20 (t, $^3J_{2\text{-}3}=^2J=8.7$ Hz, 1H, H_2), 4.54 (s, 2H, H_5), 7.26-7.37 (m, 5H, H_{arom}); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 10.4 (C_7), 26.1 (CH_2), 26.2 (CH_2), 26.4 (CH_2), 27.5 (CH), 29.3 (CH), 32.0 (CH_2), 32.4 (CH_2), 41.0 (C_9), 56.1 (C_3), 64.8 (CH_2), 68.5 (CH_2), 73.5 (C_5), 127.8 (CH), 128.0 (CH), 128.5 (CH), 137.4 (C_q), 158.1 (C_1).

Benzyldimethylvinylsilane 172



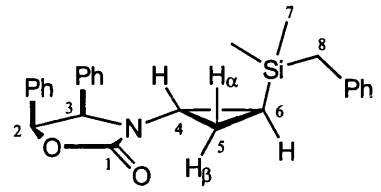
$C_{11}H_{16}Si$ 176.33 g.mol^{-1}

A solution of benzyl chloride (1.15 mL, 10 mmol, 1 eq) in dry diethyl ether (10 mL) was added dropwise to a mixture of magnesium turnings (0.24 g, 10 mmol, 1 eq) and iodine (2 crystals) in dry diethyl ether (10 mL) under nitrogen. The reaction mixture was stirred for 1 h and dimethylvinylchlorosilane (1.64 mL, 12 mmol, 1.2 eq) was added dropwise. The reaction mixture was heated at reflux for 16 h and then quenched carefully with saturated aqueous NH_4Cl solution (20 mL). The organic layer was separated and the aqueous layer was extracted with diethyl ether (2 x 20 mL). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (silica, P.E. 40-60°C) to give the *title compound* **172** (1.09 g, 6.18 mmol, 62%) as a colourless oil.

R_f (P.E. 40-60°C) 0.52; **IR** ($CDCl_3$): ν_{max} 3024 (m), 2957 (m), 2893 (w), 1601 (m), 1493 (s), 1452 (w), 1404 (m), 1248 (s), 1207 (m), 1155 (w), 1057 (w), 1009 (m), 951 (m), 831 (s, Si-C), 793 (m), 762 (m), 698 (s) cm^{-1}; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 0.57 (s, 6H, 2 x CH_3), 2.15 (s, 2H, CH_2), 5.67 (dd, $^2J_{c\text{-}b}$=3.8 Hz, $^3J_{c\text{-}a}$=20.3 Hz, 1H, H_c), 5.97 (dd, $^2J_{b\text{-}c}$=3.8 Hz, $^3J_{b\text{-}a}$=14.7 Hz, 1H, H_b), 6.13 (dd, $^3J_{a\text{-}b}$=14.7 Hz, $^3J_{a\text{-}c}$=20.3 Hz, 1H, H_a), 6.99-7.02 (m, 2H, H_{arom}), 7.05-7.09 (m, 1H, H_{arom}), 7.18-7.23 (m, 2H, H_{arom}); **^{13}C NMR** (125 MHz, $CDCl_3$): δ -3.7 (CH_3), 25.8 (CH_2), 124.0 (CH), 128.1 (CH), 128.2 (CH), 132.2 (=CH_2), 138.2 (SiCH=), 139.9 (C_q); **EI-MS** *m/z* (%): 176 (M^+, 13), 91 (Bn^+, 17), 85 ([M-Bn]$^+$, 100); **HMRS**: M^+, found 176.10155. $C_{11}H_{16}Si$ requires 176.10158.

(4*R*,5*S*)-3-[(1*S*,2*S*)-2-(Benzyldimethylsilanyl)-cyclopropyl)]-4,5-diphenyl-2-oxazolidinone (+)-173

trans isomer A



$C_{27}H_{29}NO_2Si$ 427.61 g.mol^{-1}

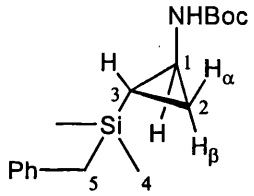
A solution of (+)-3-diethoxymethyl-4,5-diphenyl-2-oxazolidinone **(+)-109** (0.427 g, 1.25 mmol, 1.25 eq) in dry drichloromethane (1.25 mL) was added *via* a motorised syringe pump over 5.5 h to a vigorously stirred mixture of zinc amalgam (0.82 g, 12.5 mmol, 12.5 eq), zinc chloride (1M solution in diethyl ether, 1.25 mL, 1.25 mmol, 1.25 eq), chlorotrimethylsilane (0.79 mL, 6.25 mmol, 6.25 eq) and *alkene* **172** (0.176 g, 1.0 mmol, 1 eq) in dry diethyl ether (5.5 mL) under nitrogen at reflux. The mixture was stirred for 4 h and then allowed to cool to room temperature. The reaction was quenched with saturated aqueous $NaHCO_3$ solution (20 mL) and after stirring for 20 min, the mixture was filtered and the separated zinc washed with dichloromethane (20 mL). The organic solvents were removed *in vacuo* and the aqueous layer was extracted with dichloromethane (3 x 20 mL). The combined organic extracts were washed with brine (20 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude product (**(+)-173A:(+)-173B:(+)-173C:(+)-173D**: 94:<2:<2:<2 as determined by ^{1}H NMR) was purified by flash column chromatography (silica, P.E. 40-60°C/EtOAc 8.5:1.5 to 3:1) to give the cyclopropanes **(+)-173** (mixture of **(+)-173A**, **(+)-173B**, **(+)-173C**, **(+)-173D** 14 mg, 0.03 mmol, 3%, white solid; **(+)-173A** 0.179 g, 0.42 mmol, 42%, white solid; 0.45 mmol, 45%).

Isomer A: **Mp** 149-151°C (EtOAc); R_f (P.E. 40-60°C/EtOAc 3:1) 0.34; $[\alpha]_D^{18}$ +84.5 (*c* 1.06, $CHCl_3$); **IR** ($CDCl_3$): ν_{max} 3025 (w), 2921 (w), 1735 (s, C=O), 1452 (m), 1405 (m), 1247 (w), 1247 (m), 1028 (w), 846 (w), 814 (m, Si-C), 769 (w), 697 (m) cm^{-1}; **^{1}H NMR** (500 MHz, $CDCl_3$): δ -0.46 (s, 3H, H_7), -0.37 (s, 3H, H_7), -0.11 (ddd, $^3J_{6\text{-}4}$=5.0 Hz, $^3J_{6\text{-}5\alpha}$=8.3 Hz, $^3J_{6\text{-}5\beta}$=11.4 Hz, 1H, H_6), 0.83 (ddd, $^2J_{5\alpha\text{-}5\beta}$=5.0 Hz, $^3J_{5\alpha\text{-}4}$=6.3 Hz, $^3J_{5\alpha\text{-}6}$=8.2 Hz, 1H, $H_{5\alpha}$), 1.23 (ddd, $^3J_{5\beta\text{-}4}$=3.4 Hz, $^2J_{5\alpha\text{-}5\beta}$=5.0 Hz, $^3J_{5\beta\text{-}6}$=11.4 Hz, 1H,

$H_{5\beta}$), 1.81 (d, ^2J=13.6 Hz, 1H, H_8), 1.85 (d, ^2J=13.6 Hz, 1H, H_8), 2.37 (ddd, $^3J_{4\text{-}5\beta}$=3.4 Hz, $^3J_{4\text{-}6}$=5.0 Hz, $^3J_{4\text{-}5\alpha}$=6.3 Hz, 1H, H_4), 4.76 (d, $^3J_{3\text{-}2}$=8.0 Hz, 1H, H_3), 5.72 (d, $^3J_{2\text{-}3}$=8.0 Hz, 1H, H_2), 6.82-7.18 (m, 15H, H_{arom}); **^{13}C NMR** (125 MHz, $CDCl_3$): δ -5.3 (C_7), -4.8 (C_7), 4.1 (C_6), 11.6 (C_5), 24.8 (C_8), 29.0 (C_4), 66.9 (C_3), 79.6 (C_2), 124.0 (CH), 125.9 (CH), 127.6 (CH), 127.8 (CH), 128.0 (CH), 128.1 (CH), 128.2 (CH), 128.3 (CH), 134.3 (C_q), 134.4 (C_q), 139.4 (C_q), 158.4 (C_1); **CI(ammonia)-MS** *m/z* (%): 426 ($[M\text{-}H]^+$, 29), 382 ($[M\text{-}H\text{-}CO_2]^+$, 100), 308 (26), 238 (16), 195 (57); **HMRS**: $(M\text{-}H)^+$, found 426.18798. $C_{27}H_{28}NO_2Si$ requires 426.18892; **Anal.** found: C, 76.09; H, 6.93; N, 3.30. Calcd for $C_{27}H_{29}NO_2Si$: C, 75.84; H, 6.84; N, 3.38.

For the crystallographic details of **(+)-173**, see **Appendix**.

tert-Butyl *N*-[(1*S*,2*S*)-2-(Benzyldimethylsilanyl)-cyclopropyl)]carbamate (+)-174



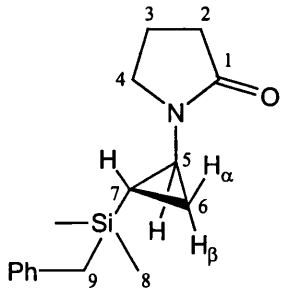
$C_{17}H_{27}NO_2Si$ 305.48 g.mol^{-1}

A mixture of cyclopropane **(+)-173A** (100 mg, 0.234 mmol, 1 eq), di-*tert*-butyl dicarbonate (102 mg, 0.468 mmol, 2 eq), $Pd(OH)_2/C$ (20%, 52 wt. % water, 51 mg, 0.036 mmol, 0.15 eq) and THF (8 mL) was hydrogenated at 5.5 bar at 30°C for 8 h. The reaction mixture was filtered, concentrated *in vacuo* and purified by flash column chromatography (silica, P.E. 40-60°C/diethyl ether 9:1 to 4:1) to give the *title compound* **(+)-174** (57 mg, 0.187 mmol, 80%) as a colourless oil.

R_f (P.E. 40-60°C/ether 4:1) 0.31; $[\alpha]_D^{18}$ +16.3 (*c* 1.0, $CHCl_3$); **IR** (film): ν_{max} 3327 (br, NH), 2976 (m), 2895 (w), 1705 (s, C=O), 1493 (s), 1452 (m), 1365 (s), 1247 (s), 1171 (s), 1078 (m), 833 (s, Si-C), 791 (w), 700 (s) cm^{-1}; **^{1}H NMR** (400 MHz, 328 K, $CDCl_3$): δ -0.28 (ddd, $^3J_{3\text{-}1}$=4.9 Hz, $^3J_{3\text{-}2\beta}$=8.1 Hz, $^3J_{3\text{-}2\alpha}$=11.2 Hz, 1H, H_6), -0.09 (s, 3H, H_4), -0.06 (s, 3H, H_4), 0.57 (ddd, $^2J_{2\beta\text{-}2\alpha}$=4.7 Hz, $^3J_{2\beta\text{-}1}$=6.4 Hz, $^3J_{2\beta\text{-}3}$=8.1 Hz, 1H, $H_{2\beta}$), 0.69 (ddd, $^3J_{2\alpha\text{-}1}$=3.3 Hz, $^2J_{2\alpha\text{-}2\beta}$=4.7 Hz, $^3J_{2\alpha\text{-}3}$=11.2 Hz, 1H, $H_{2\alpha}$), 1.44 (s, 9H, $C(CH_3)_3$), 2.11 (d, ^2J=13.6 Hz, 1H, H_5), 2.15 (d, ^2J=13.6 Hz, 1H, H_5), 2.46 (ddd, $^3J_{1\text{-}2\alpha}$=3.3 Hz,

$^3J_{1\text{-}3}$=8.1 Hz, $^3J_{1\text{-}2\beta}$=6.2 Hz, 1H, H_1), 4.53 (br s, 1H, NH), 7.00-7.07 (m, 3H, H_{arom}), 7.15-7.21 (m, 2H, H_{arom}); **^{13}C NMR** (100 MHz, 328 K, $CDCl_3$): δ -4.5 (2 x C_4), 5.8 (C_3), 10.6 (C_2), 25.5 (C_5), 27.2 (C_1), 28.5 ($C(CH_3)_3$), 79.3 ($C(CH_3)_3$), 124.1 (CH), 128.1 (CH), 128.2 (CH), 140.0 (C_q), 156.4 (C=O); **EI-MS** *m/z* (%): 305 (M^+, 5), 249 ([M+H-C_4H_9]$^+$, 22), 204 ([M-Boc]$^+$, 43), 149 (100), 114 (100), 98 (42), 75 (22); **HMRS**: M^+, found 305.18162. $C_{17}H_{27}NO_2Si$ requires 305.18110.

1-[2-(Benzyldimethylsilanyl)-cyclopropyl)]-2-pyrrolidinone 175



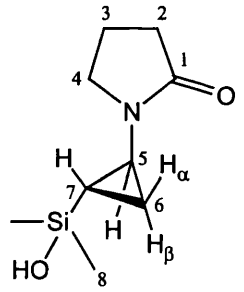
$C_{16}H_{23}NOSi$ 273.45 g.mol^{-1}

A solution of *N*-diethoxymethy-2-pyrrolidinone **78** (1.5 g, 8.0 mmol, 2 eq) in dry diethyl ether (8 mL) was added *via* a motorised syringe pump over 6 h to a vigorously stirred mixture of zinc amalgam (5.23 g, 80 mmol, 20 eq), zinc chloride (1M solution in diethyl ether, 8 mL, 8 mmol, 2 eq), chlorotrimethylsilane (5.08 mL, 40 mmol, 10 eq) and *alkene* **172** (0.705 g, 4 mmol, 1 eq) in dry diethyl ether (16 mL) under nitrogen at reflux. The mixture was stirred for 18 h and then allowed to cool to room temperature. The reaction was quenched with saturated aqueous $NaHCO_3$ solution (30 mL) and after stirring for 20 min, the mixture was filtered and the separated zinc washed with diethyl ether (20 mL). The organic layer was separated and the aqueous layer was extracted with diethyl ether (2 x 30 mL). The combined organic extracts were washed with brine (30 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude product (*trans/cis*: >95:<5 as determined by ^{1}H NMR) was purified by flash column chromatography (silica, EtAOc/P.E. 40-60°C 4:1) to give almost exclusively the *trans* cyclopropane **175** (0.422 g, 1.54 mmol, 39%) as a colourless oil.

R_f (EtOAc) 0.41; **IR** (film): ν_{max} 2953 (m), 2891 (w), 1689 (s, C=O), 1493 (m), 1419 (m), 1294 (m), 1248 (m), 1155 (w), 883 (m, Si-C), 833 (s, Si-C), 791 (m), 700 (m) cm^{-1};

^{1}H NMR (500 MHz, $CDCl_3$): δ -0.10 (s, 3H, H_8), -0.08 (ddd, $^3J_{7\text{-}5}$=5.3 Hz, $^3J_{7\text{-}6\beta}$=8.2 Hz, $^3J_{7\text{-}6\alpha}$=11.3 Hz, 1H, H_7), -0.05 (s, 3H, H_8), 0.64 (ddd, $^2J_{6\beta\text{-}6\alpha}$=5.0 Hz, $^3J_{6\beta\text{-}5}$=6.7 Hz, $^3J_{6\beta\text{-}7}$=8.2 Hz, 1H, $H_{6\beta}$), 0.92 (ddd, $^3J_{6\alpha\text{-}5}$=3.7 Hz, $^2J_{6\alpha\text{-}6\beta}$=5.0 Hz, $^3J_{6\alpha\text{-}7}$=11.3 Hz, 1H, $H_{5\alpha}$), 1.87-1.95 (m, 2H, H_3), 2.13 (s, 2H, H_9), 2.34 (t, $^3J_{2\text{-}3}$=8.0 Hz, 2H, H_2), 2.61 (ddd, $^3J_{5\text{-}6\alpha}$=3.7 Hz, $^3J_{5\text{-}7}$=5.3 Hz, $^3J_{5\text{-}6\beta}$=6.7 Hz, 1H, H_5), 3.16 (t, $^3J_{4\text{-}3}$=7.0 Hz, 2H, H_4), 6.99-7.06 (m, 3H, H_{arom}), 7.15-7.20 (m, 2H, H_{arom}); **^{13}C NMR** (125 MHz, $CDCl_3$): δ -4.8 (C_8), -4.6 (C_8), 2.7 (C_7), 8.4 (C_6), 18.0 (C_3), 25.2 (C_9), 29.1 (C_5), 31.9 (C_2), 47.0 (C_4), 124.0 (CH), 128.1 (CH), 128.2 (CH), 139.8 (C_q), 175.9 (C_1); **EI-MS** *m/z* (%): 273 (M^+, 62), 258 ([M-CH_3]$^+$, 24), 218 (24), 182 ([M-Bn]$^+$, 92), 149 (100), 121 (86), 97 (31), 91 (Bn^+, 23); **HMRS**: M^+, found 273.15083. $C_{16}H_{23}NOSi$ requires 273.15488.

1-[2-(Hydroxymethylsilanyl)-cyclopropyl)]-2-pyrrolidinone 176



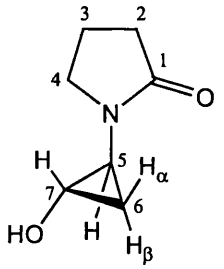
$C_9H_{17}NO_2Si$ 199.33 g.mol^{-1}

Tetrabutylammonium fluoride (1M solution in THF, 4.79 mL, 4.79 mmol, 2.2 eq) was added to a solution of cyclopropane **175** (0.6 g, 2.18 mmol, 1 eq) in THF (3.9 mL) at 4°C. After 10 min of stirring, the reaction mixture was quenched with brine (10 mL). The aqueous layer was extracted with diethyl ether (10 mL) and EtOAc (3 x 10 mL). The combined organic extracts were dried (Na_2SO_4), filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (silica, EtOAc/MeOH 9.5:0.5 to 9:1) to give the silanol **176** pure at 95 % (0.2 g, 1.0 mmol, 46%) as a colourless oil.

R_f (EtOAc/MeOH 9:1) 0.4; **IR** (film): ν_{max} 3365 (br, OH), 2955 (s), 2895 (m), 1682 (s, C=O), 1464 (m), 1423 (s), 1375 (m), 1296 (m), 1254 (s), 1059 (s), 886 (s, Si-C), 829 (s, Si-C), 787 (s) cm^{-1}; **^{1}H NMR** (500 MHz, $CDCl_3$): δ -0.07 (m, 1H, H_7), -0.03 (s, 3H,

H_8), 0.08 (s, 3H, H_8), 0.63-0.72 (m, 1H, H_6), 0.81-0.92 (m, 1H, H_6), 1.83-1.96 (m, 2H, H_3), 2.30 (t, $^3J_{2\text{-}3}$=8.0 Hz, 2H, H_2), 2.56-2.65 (m, 1H, H_5), 3.23 (t, $^3J_{4\text{-}3}$=7.0 Hz, 2H, H_4), 4.79 (br s, 1H, OH); **^{13}C NMR** (75 MHz, $CDCl_3$): δ -1.9 (C_8), -0.8 (C_8), 6.0 (C_7), 8.1 (C_6), 18.0 (C_3), 28.8 (C_5), 31.9 (C_2), 47.3 (C_4), 176.6 (C_1); **EI-MS** *m/z* (%): 199 (M^+, 100), 184 ([M-CH_3]$^+$, 53), 144 (54), 124 (54), 124 (26), 96 (16), 75 (63); **HMRS**: M^+, found 199.10127. $C_9H_{17}NO_2Si$ requires 199.10285.

1-[2-(Hydroxycyclopropyl)]-2-pyrrolidinone 180



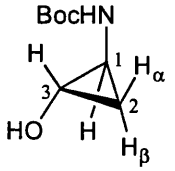
$C_7H_{11}NO_2$ 141.17 g.mol^{-1}

Tetrabutylammonium fluoride (1M solution in THF, 1.09 mL, 1.09 mmol, 2 eq) was added to a solution of cyclopropane **175** (0.15 g, 0.544 mmol, 1 eq) in THF (0.3 mL) under nitrogen. After 30 min of stirring, methanol (1.4 mL), potassium hydrogencarbonate (0.11 g, 1.09 mmol, 2 eq) and hydrogen peroxide (30% solution in water, 1.12 mL, 10.9 mmol, 20 eq) were added to the solution. The reaction mixture was stirred for 18 h and then sodium thiosulfate pentahydrate (2.97 g, 11.97 mmol, 22 eq) was added. After stirring for 30 min the mixture was filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (silica, EtOAc/MeOH 1:0 to 9:1) to give the *title compound* **180** (27 mg, 0.191 mmol, 35%) as a colourless oil.

R_f (EtOAc/MeOH 9:1) 0.35; **IR** (film): ν_{max} 3369 (br, OH), 2989 (w), 2957 (w), 2859 (w), 1662 (s, C=O), 1463 (m), 1425 (m), 1300 (s), 1202 (m), 1155 (w), 1020 (w), 927 (w) cm^{-1}; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 0.83 (dt, $^3J_{6\alpha\text{-}5}$=5.0 Hz, $^2J_{6\alpha\text{-}6\beta}$=$^3J_{6\alpha\text{-}7}$=7.1 Hz, 1H, $H_{6\alpha}$), 1.02 (ddd, $^3J_{6\beta\text{-}7}$=4.1 Hz, $^2J_{6\beta\text{-}6\alpha}$=7.1 Hz, $^3J_{6\beta\text{-}5}$=8.8 Hz, 1H, $H_{6\beta}$), 1.85-1.99 (m, 2H, H_3), 2.33 (t, $^3J_{2\text{-}3}$=8.1 Hz, 2H, H_2), 2.53 (ddd, $^3J_{5\text{-}7}$=1.6 Hz, $^3J_{5\text{-}6\alpha}$=5.0 Hz, $^3J_{5\text{-}6\beta}$=8.6 Hz, 1H, H_5), 3.20-3.30 (m, 2H, H_4), 3.50 (ddd, $^3J_{7\text{-}5}$=1.6 Hz, $^3J_{7\text{-}6\beta}$=4.1 Hz,

$^3J_{7\text{-}6\alpha}$=7.5 Hz, 1H, H_7), 4.31 (br s, 1H, OH); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 14.6 (C_6), 17.9 (C_3), 31.6 (C_2), 32.4 (C_5), 47.4 (C_4), 51.1 (C_7), 176.6 (C_1); **EI-MS** *m/z* (%): 141 (M^+, 7), 112 (100), 98 (24), 84 (23), 69 (47); **HMRS**: M^+, found 141.07832. $C_7H_{11}NO_2$ requires 141.07843.

tert-Butyl _N_-[(1_S_,2_S_)-2-(Hydroxycyclopropyl)]carbamate (+)-181

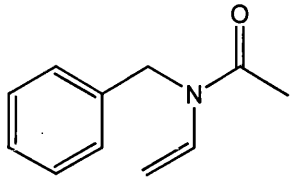


$C_8H_{15}NO_3$ 173.21 g.mol^{-1}

Tetrabutylammonium fluoride (1M solution in THF, 0.33 mL, 0.33 mmol, 2 eq) was added to a solution of cyclopropane **(+)-174** (50 mg, 0.164 mmol, 1 eq) in THF (0.08 mL) under nitrogen. After 30 min of stirring, methanol (0.41 mL), potassium hydrogencarbonate (32.8 mg, 0.33 mmol, 2 eq) and hydrogen peroxide (30% solution in water, 0.34 mL, 3.28 mmol, 20 eq) were added to the solution. The reaction mixture was stirred for 16 h and then sodium thiosulfate pentahydrate (0.9 g, 3.62 mmol, 22 eq) was added. After stirring for 30 min the mixture was filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (silica, P.E. 40-60°C/EtOAc 4:1 to 1:1) to give the *title compound* **(+)-181** (25 mg, 0.144 mmol, 88%) as a colourless oil.

***R*$_f$** (P.E. 40-60°C/EtOAc 1:1) 0.3; $[\alpha]_D^{25}$ -14.6 (*c* 0.99, $CHCl_3$); **IR** (film): ν_{max} 3327 (br, NH), 2978 (m), 2931 (w), 1690 (s, C=O), 1522 (m), 1367 (m), 1278 (m), 1256 (m), 1171 (s), 1020 (w) cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 0.71 (dt, $^3J_{2\alpha\text{-}1}$=4.6 Hz, $^2J_{2\alpha\text{-}2\beta}$=$^3J_{2\alpha\text{-}3}$=7.0 Hz, 1H, $H_{2\alpha}$), 0.99 (ddd, $^3J_{2\beta\text{-}3}$=3.9 Hz, $^2J_{2\beta\text{-}2\alpha}$=6.8 Hz, $^3J_{2\beta\text{-}1}$=8.5 Hz, 1H, $H_{2\beta}$), 1.40 (s, 9H, $C(CH_3)_3$), 2.48-2.54 (m, 1H, H_1), 3.36 (ddd, $^3J_{3\text{-}1}$=1.4 Hz, $^3J_{3\text{-}2\beta}$=3.9 Hz, $^3J_{3\text{-}2\alpha}$=7.2 Hz, 1H, H_3), 4.09 (br s, 1H, OH), 4.68 (br s, 1H, NH); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 15.7 (C_2), 28.3 ($C(CH_3)$), 30.5 (C_1), 52.6 (C_3), 79.9 ($C(CH_3)$), 156.7 (C=O); **EI-MS** *m/z* (%): 173 (M^+, 100); **HMRS**: M^+, found 173.10521. $C_8H_{15}NO_3$ requires 173.10519.

_N_-Benzyl-_N_-vinylacetamide 188

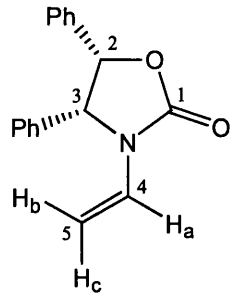


$C_{11}H_{13}NO$ 175.23 $g.mol^{-1}$

_N_-vinyl acetamide (1.36 g, 16.0 mmol, 1 eq) was added portionwise to a suspension of NaH (60% in oil, 1.28 g, 32.0 mmol, 2 eq) in dry DMF (32 mL) under nitrogen. The reaction mixture was stirred for 30 min and benzyl bromide (5.71 mL, 48 mmol, 3 eq) was added dropwise. After stirring for 4 h, the reaction was carefully quenched with saturated aqueous NH_4Cl solution (30 mL). Diethyl ether (60 mL) was added and the mixture transfered into a separating funnel. The organic layer was separated and the aqueous layer was extracted with diethyl ether (2 x 30 mL). The combined organic extracts were washed with brine (30 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (silica, P.E. 40-60°C/EtOAc 4:1 to 3:2) to give the *title compound* **188** (1.79 g, 10.2 mmol, 64%) as a yellow oil.

R_f (P.E. 40-60°C/EtOAc 1:1) 0.60; **IR** (film): ν_{max} 3032 (m), 2931 (w), 1674 (s, C=O), 1622 (s), 1420 (m), 1383 (s), 1342 (m), 1213 (m), 1028 (w), 847 (w), 727 (m), 696 (w) cm^{-1}; **^{1}H NMR** (400 MHz, 373 K, DMSO): δ 2.22 (s, 3H, CH_3), 4.34 (d, ^3J=9.2 Hz, 1H, $=CH_2$), 4.47 (d, ^3J=15.6 Hz, 1H, $=CH_2$), 4.85 (s, 2H, $PhCH_2N$), 7.15 (dd, ^3J=9.2 Hz, ^3J=15.6 Hz, 1H, NCH=), 7.20-7.36 (m, 5H, H_{arom}); **^{13}C NMR** (100 MHz, 373 K, DMSO): δ 20.9 (CH_3), 45.4 (CH_2), 93.8 ($=CH_2$), 125.7 (CH), 126.0 (CH), 127.5 (CH), 132.9 (NCH=), 136.7 (C_q), 168.4 (C=O); **EI-MS** *m/z* (%): 175 (M^+, 86), 148 ($[M-C_2H_3]^+$, 27), 132 ($[M-COCH_3]^+$, 100), 117 (19), 106 (56).

(4*R*,5*S*)-4,5-Diphenyl-3-vinyl-2-oxazolidinone (+)-189



$C_{17}H_{15}NO_2$ 265.31 g.mol^{-1}

(4*R*,5*S*)-3-(1-Ethoxyethyl)-4,5-diphenyl-2-oxazolidinone

The *N,O*-acetal was prepared by a modification of the literature method.[144] A mixture of oxazolidinone **(+)-112** (1.24 g, 5.18 mmol, 1 eq), 10-camphorsulfonic acid (0.09 g, 0.39 mmol, 0.075 eq) and acetaldehyde diethylacetal (11 mL, 77.7 mmol, 15 eq) was heated at 60°C for 24 h. The reaction mixture was cooled to room temperature and then quenched with saturated aqueous $NaHCO_3$ solution (10 mL). The aqueous phase was extracted with diethyl ether (40 mL then 20 mL) and the combined organic extracts were washed with brine (15 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo* to give the expected *N,O*-acetal (1.48 g, 5.18 mmol, 100%, 2/3:1/3 mixture of diastereoisomers) as a yellow oil which was used without further purification.

Major isomer: **^{1}H NMR** (500 MHz, $CDCl_3$): δ 0.89 (d, ^3J=6.4 Hz, 3H, C*H*$_3$CH), 1.23 (t, ^3J=7.1 Hz, 3H, C*H*$_3$CH$_2$), 3.51 (qd, ^3J=7.1 Hz, ^2J=9.4 Hz, 1H, C*H*HCH3), 3.68 (qd, ^3J=7.1 Hz, ^2J=9.4 Hz, 1H, CH*H*CH3), 5.04 (d, ^3J=7.9 Hz, 1H, NCHPh), 5.41 (q, ^3J=6.4 Hz, 1H, C*H*CH$_3$), 5.82 (d, ^3J=7.9 Hz, 1H, OCHPh), 6.82-7.02 (m, 10H, H_{arom}); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 14.9 (CH_3), 20.6 (CH_3), 59.8 (NCHPh), 63.4 (*C*H$_2$CH3), 80.8 (CH), 80.9 (CH), 125.8 (CH), 127.2 (CH), 127.5 (CH), 127.6 (CH), 127.7 (CH), 127.8 (CH), 133.8 (C_q), 136.4 (C_q), 158.1 (C=O).

(4*R*,5*S*)-4,5-Diphenyl-3-vinyl-2-oxazolidinone (+)-189

Trimethylsilyl trifluoromethanesulfonate (0.68 mL, 3.55 mmol, 1.3 eq) was added dropwise to a solution of the crude *N,O*-acetal (0.78 g, 2.5 mmol, 1 eq) and

triethylamine (0.57 mL, 4.1 mmol, 1.5 eq) in dry dichloromethane (5 mL) under nitrogen at 4°C. The reaction mixture was allowed to warm to room temperature and stirred for 24 h. The mixture was cooled to 4°C and saturated aqueous $NaHCO_3$ solution (5 mL) was added. After stirring for 5 min, the mixture was transferred into a separating funnel. The organic layer was separated and the aqueous layer was extracted with dichloromethane (5 mL). The combined organic extracts were washed with brine (5 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (silica, P.E. 40-60°C/EtOAc 4:1) to give the *title compound* **(+)-189** (0.44 g, 1.66 mmol, 67%) as a white solid.

Mp 166-167°C (lit.,[13] 170-171°C (EtOAc/hexane); R_f (P.E. 40-60°C/EtOAc 4:1) 0.36; $[\alpha]_D^{31}$ +22.0 (*c* 1.0, $CHCl_3$) (lit.,[13] $[\alpha]_D^{20}$ +21.7 (*c* 0.775, $CHCl_3$); **IR** (film): ν_{max} 3070 (w), 3034 (w), 1763 (s, C=O), 1640 (s), 1558 (s), 1456 (m), 1425 (m), 1382 (m), 1364 (m), 1217 (m), 1103 (w), 1043 (w), 908 (s), 733 (s) cm^{-1}; **^{1}H NMR** (500 MHz, $CDCl_3$): δ4.07 (dd, $^2J_{b\text{-}c}$=1.0 Hz, $^3J_{b\text{-}a}$=16.0 Hz, 1H, H_b), 4.34 (dd, $^2J_{c\text{-}b}$=1.0 Hz, $^3J_{c\text{-}a}$=9.1 Hz, 1H, H_c), 5.24 (d, $^3J_{3\text{-}2}$=8.1 Hz, 1H, H_3), 5.82 (d, $^3J_{2\text{-}3}$=8.1 Hz, 1H, H_2), 6.79-6.87 (m, 2H, H_{arom}), 6.90-6.93 (m, 2H, H_{arom}), 6.94 (dd, $^3J_{a\text{-}c}$=9.1 Hz, $^3J_{a\text{-}b}$=16.0 Hz, 1H, H_a), 7.05-7.08 (m, 6H, H_{arom}); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 63.1 (C_3), 80.5 (C_2), 96.2 (C_5), 126.3 (CH), 127.0 (CH), 127.9 (CH), 128.2 (CH), 128.3 (CH), 128.6 (CH), 133.2 (C_q), 133.6 (C_q), 155.3 (C_1); **EI-MS** *m/z* (%): 265 (M^+, 44), 220 (12), 180 (37), 168 (22), 131 (77), 104 (100); **HMRS**: M^+, found 265.11056. $C_{17}H_{15}NO_2$ requires 265.11027.

Chapter 5

References

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Chapter 6

Appendix

Table A. Crystal data and structure refinement for **(+)-173A**.

Chemical formula	$C_{27}H_{29}NO_2Si$	
Formula weight	427.60	
Temperature	150(2) K	
Radiation, wavelength	MoKα, 0.71073 Å	
Crystal system, space group	orthorhombic, $P2_12_12_1$	
Unit cell parameters	a = 6.5393(8) Å	α = 90°
	b = 13.7564(16) Å	β = 90°
	c = 26.057(3) Å	γ = 90°
Cell volume	2344.0(5) $Å^3$	
Z	4	
Calculated density	1.212 g/cm^3	
Absorption coefficient μ	0.123 mm^{-1}	
F(000)	912	
Crystal colour and size	colourless, 0.50 × 0.24 × 0.22 mm^3	
Data collection method	Bruker SMART APEX diffractometer	
	ω rotation with narrow frames	
θ range for data collection	1.56 to 28.31°	
Index ranges	h −8 to 8, k −18 to 18, l −34 to 34	
Completeness to θ = 26.00°	99.7 %	
Reflections collected	20365	
Independent reflections	5568 (R_{int} = 0.0363)	
Reflections with $F^2>2\sigma$	5427	
Absorption correction	semi-empirical from equivalents	
Min. and max. transmission	0.9409 and 0.9734	
Structure solution	direct methods	
Refinement method	Full-matrix least-squares on F^2	
Weighting parameters a, b	0.0586, 9.9841	
Data / restraints / parameters	5568 / 0 / 281	
Final R indices [$F^2>2\sigma$]	R1 = 0.1139, wR2 = 0.2619	
R indices (all data)	R1 = 0.1156, wR2 = 0.2628	
Goodness-of-fit on F^2	1.173	
Extinction coefficient	0.0032(15)	
Largest and mean shift/su	0.003 and 0.000	
Largest diff. peak and hole	1.161 and −0.470 e $Å^{-3}$	

Table B. Atomic coordinates and equivalent isotropic displacement parameters ($Å^2$) for **(+)-173A**. U_{eq} is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U_{eq}
Si(1)	0.0501(3)	0.26869(11)	0.18200(6)	0.0304(4)
N(1)	0.3979(7)	0.1695(3)	0.06087(17)	0.0284(10)
O(1)	0.5661(7)	0.0934(3)	−0.00121(15)	0.0431(12)
O(2)	0.7356(8)	0.2052(4)	0.04546(18)	0.0560(15)
C(1)	0.5807(10)	0.1616(5)	0.0370(2)	0.0401(15)
C(2)	0.3502(10)	0.0675(4)	−0.0062(2)	0.0315(12)
C(3)	0.2617(9)	0.0893(4)	0.04784(18)	0.0263(10)
C(4)	0.3285(9)	−0.0358(4)	−0.02520(18)	0.0292(11)
C(5)	0.1408(9)	−0.0638(4)	−0.0444(2)	0.0316(12)
C(6)	0.1071(11)	−0.1583(5)	−0.0622(2)	0.0425(15)
C(7)	0.2657(11)	−0.2238(4)	−0.0598(2)	0.0389(13)
C(8)	0.4547(13)	−0.1973(5)	−0.0413(2)	0.0453(16)
C(9)	0.4847(10)	−0.1021(5)	−0.0235(2)	0.0374(14)
C(10)	0.2732(9)	0.0064(4)	0.08634(18)	0.0261(11)
C(11)	0.4552(12)	−0.0145(6)	0.1124(2)	0.0513(18)
C(12)	0.4652(17)	−0.0897(7)	0.1477(3)	0.073(3)
C(13)	0.293(2)	−0.1432(6)	0.1578(3)	0.069(3)
C(14)	0.1100(19)	−0.1242(5)	0.1323(3)	0.074(3)
C(15)	0.1025(11)	−0.0479(4)	0.0972(2)	0.0390(15)
C(16)	0.3698(8)	0.2272(4)	0.10656(18)	0.0268(10)
C(17)	0.3477(10)	0.3346(4)	0.1017(2)	0.0320(12)
C(18)	0.1676(8)	0.2716(4)	0.11654(19)	0.0286(11)
C(19)	0.2353(10)	0.3119(4)	0.2308(2)	0.0345(13)
C(20)	−0.1827(10)	0.3449(6)	0.1837(3)	0.0527(18)
C(21)	−0.0229(13)	0.1386(5)	0.1932(2)	0.0483(19)
C(22)	−0.1165(8)	0.1143(4)	0.2437(2)	0.0275(11)
C(23)	0.0031(18)	0.1111(5)	0.2866(3)	0.072(3)
C(24)	−0.039(2)	0.0868(8)	0.3345(4)	0.088(3)
C(25)	−0.2259(15)	0.0814(7)	0.3410(4)	0.069(3)
C(26)	−0.3905(14)	0.0762(5)	0.3078(4)	0.075(3)
C(27)	−0.3227(12)	0.0982(6)	0.2506(5)	0.081(3)

Table C. Bond lengths [Å] and angles [°] for **(+)-173A**.

Si(1)–C(20)	1.849(7)	Si(1)–C(19)	1.854(6)
Si(1)–C(18)	1.871(5)	Si(1)–C(21)	1.875(6)
N(1)–C(1)	1.352(8)	N(1)–C(16)	1.443(6)
N(1)–C(3)	1.457(7)	O(1)–C(1)	1.371(7)
O(1)–C(2)	1.462(7)	O(2)–C(1)	1.197(7)
C(2)–C(4)	1.511(8)	C(2)–C(3)	1.551(7)
C(3)–C(10)	1.521(7)	C(4)–C(9)	1.370(8)
C(4)–C(5)	1.380(8)	C(5)–C(6)	1.398(8)
C(6)–C(7)	1.376(9)	C(7)–C(8)	1.376(10)
C(8)–C(9)	1.403(9)	C(10)–C(15)	1.373(8)
C(10)–C(11)	1.400(9)	C(11)–C(12)	1.387(11)
C(12)–C(13)	1.371(14)	C(13)–C(14)	1.393(14)
C(14)–C(15)	1.393(10)	C(16)–C(18)	1.479(8)
C(16)–C(17)	1.489(8)	C(17)–C(18)	1.512(7)
C(21)–C(22)	1.489(8)	C(22)–C(23)	1.365(10)
C(22)–C(27)	1.378(9)	C(23)–C(24)	1.323(13)
C(24)–C(25)	1.233(15)	C(25)–C(26)	1.382(14)
C(26)–C(27)	1.585(15)		

C(20)–Si(1)–C(19)	109.8(3)	C(20)–Si(1)–C(18)	110.4(3)
C(19)–Si(1)–C(18)	110.5(3)	C(20)–Si(1)–C(21)	109.1(4)
C(19)–Si(1)–C(21)	111.5(3)	C(18)–Si(1)–C(21)	105.5(3)
C(1)–N(1)–C(16)	122.4(5)	C(1)–N(1)–C(3)	111.9(5)
C(16)–N(1)–C(3)	122.1(4)	C(1)–O(1)–C(2)	107.4(5)
O(2)–C(1)–N(1)	128.6(6)	O(2)–C(1)–O(1)	122.3(6)
N(1)–C(1)–O(1)	109.1(5)	O(1)–C(2)–C(4)	110.5(5)
O(1)–C(2)–C(3)	103.5(4)	C(4)–C(2)–C(3)	116.4(4)
N(1)–C(3)–C(10)	112.5(4)	N(1)–C(3)–C(2)	97.5(4)
C(10)–C(3)–C(2)	115.8(4)	C(9)–C(4)–C(5)	119.3(5)
C(9)–C(4)–C(2)	123.0(5)	C(5)–C(4)–C(2)	117.7(5)
C(4)–C(5)–C(6)	121.3(5)	C(7)–C(6)–C(5)	118.4(6)
C(8)–C(7)–C(6)	121.3(6)	C(7)–C(8)–C(9)	119.3(6)
C(4)–C(9)–C(8)	120.4(6)	C(15)–C(10)–C(11)	118.7(6)
C(15)–C(10)–C(3)	120.2(5)	C(11)–C(10)–C(3)	121.1(6)
C(12)–C(11)–C(10)	121.0(8)	C(13)–C(12)–C(11)	119.3(8)
C(12)–C(13)–C(14)	120.9(7)	C(13)–C(14)–C(15)	119.0(8)
C(10)–C(15)–C(14)	121.1(8)	N(1)–C(16)–C(18)	119.1(4)
N(1)–C(16)–C(17)	119.2(4)	C(18)–C(16)–C(17)	61.3(4)
C(16)–C(17)–C(18)	59.1(4)	C(16)–C(18)–C(17)	59.7(4)
C(16)–C(18)–Si(1)	121.2(4)	C(17)–C(18)–Si(1)	124.4(4)
C(22)–C(21)–Si(1)	117.1(4)	C(23)–C(22)–C(27)	116.6(8)
C(23)–C(22)–C(21)	119.7(7)	C(27)–C(22)–C(21)	123.7(8)
C(24)–C(23)–C(22)	131.4(11)	C(25)–C(24)–C(23)	110.6(11)
C(24)–C(25)–C(26)	133.5(11)	C(25)–C(26)–C(27)	111.1(8)
C(22)–C(27)–C(26)	115.4(9)		

Table D. Anisotropic displacement parameters ($Å^2$) for **(+)-173A**. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U^{11} + ...+ 2hka^*b^*U^{12}]$

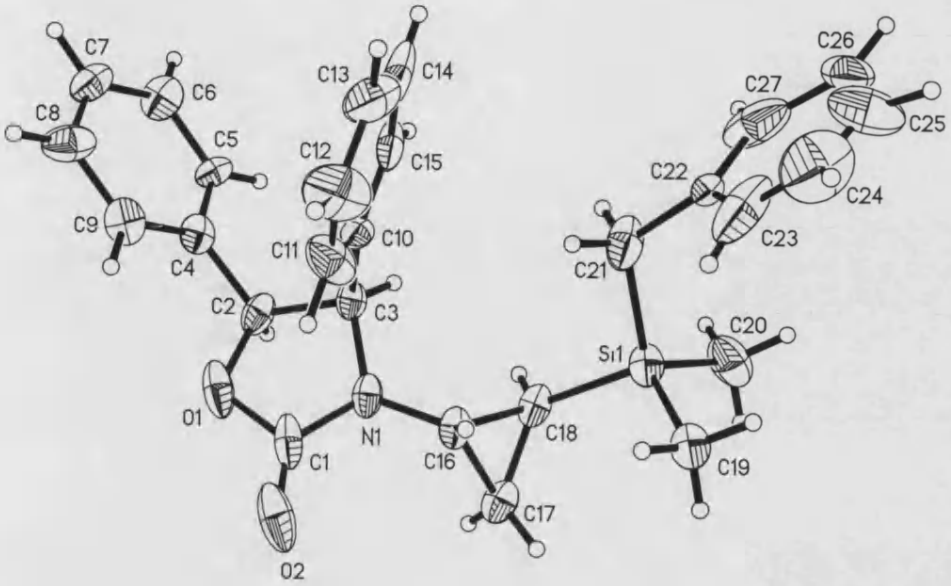
	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
Si(1)	0.0367(8)	0.0284(7)	0.0262(7)	−0.0061(6)	0.0011(7)	−0.0107(7)
N(1)	0.033(2)	0.030(2)	0.023(2)	−0.0015(17)	0.0000(18)	−0.0142(19)
O(1)	0.049(3)	0.052(3)	0.029(2)	−0.0155(18)	0.016(2)	−0.028(2)
O(2)	0.046(3)	0.079(4)	0.043(3)	−0.021(2)	0.014(2)	−0.040(3)
C(1)	0.046(4)	0.049(3)	0.025(3)	−0.002(2)	0.012(3)	−0.022(3)
C(2)	0.046(3)	0.028(3)	0.020(2)	0.003(2)	−0.004(2)	−0.007(2)
C(3)	0.031(3)	0.030(3)	0.018(2)	0.0019(19)	−0.001(2)	−0.004(2)
C(4)	0.037(3)	0.037(3)	0.014(2)	0.000(2)	−0.003(2)	−0.001(2)
C(5)	0.038(3)	0.022(2)	0.035(3)	0.005(2)	−0.003(2)	0.005(2)
C(6)	0.048(4)	0.040(3)	0.039(3)	−0.002(3)	−0.008(3)	−0.008(3)
C(7)	0.059(4)	0.026(3)	0.032(3)	0.002(2)	−0.004(3)	0.001(3)
C(8)	0.062(4)	0.040(3)	0.034(3)	−0.006(3)	−0.008(3)	0.017(3)
C(9)	0.034(3)	0.050(4)	0.029(3)	−0.001(3)	−0.008(2)	−0.006(3)
C(10)	0.043(3)	0.017(2)	0.018(2)	−0.0032(18)	0.006(2)	0.004(2)
C(11)	0.047(4)	0.080(5)	0.028(3)	0.006(3)	0.004(3)	0.020(4)
C(12)	0.090(7)	0.098(7)	0.032(3)	0.012(4)	−0.011(4)	0.041(6)
C(13)	0.142(10)	0.041(4)	0.026(3)	0.003(3)	0.018(5)	0.026(5)
C(14)	0.151(10)	0.036(4)	0.033(3)	−0.004(3)	0.028(5)	−0.050(5)
C(15)	0.058(4)	0.032(3)	0.027(3)	0.000(2)	0.013(3)	−0.022(3)
C(16)	0.033(3)	0.030(3)	0.017(2)	−0.002(2)	−0.0030(19)	−0.008(2)
C(17)	0.045(3)	0.023(2)	0.028(3)	−0.004(2)	−0.005(2)	−0.011(2)
C(18)	0.037(3)	0.027(2)	0.022(2)	0.000(2)	−0.007(2)	−0.012(2)
C(19)	0.039(3)	0.033(3)	0.032(3)	−0.006(2)	0.002(3)	−0.009(3)
C(20)	0.031(3)	0.077(5)	0.050(4)	−0.002(4)	0.005(3)	−0.001(3)
C(21)	0.083(5)	0.034(3)	0.028(3)	−0.006(2)	0.012(3)	−0.020(3)
C(22)	0.031(3)	0.019(2)	0.032(3)	0.0044(19)	0.006(2)	0.001(2)
C(23)	0.121(9)	0.043(4)	0.053(4)	0.018(3)	−0.028(5)	−0.019(5)
C(24)	0.116(9)	0.086(7)	0.063(6)	−0.005(5)	−0.031(6)	0.001(7)
C(25)	0.061(5)	0.067(5)	0.080(6)	−0.041(5)	−0.012(5)	0.015(5)
C(26)	0.067(5)	0.026(3)	0.130(8)	0.004(4)	0.061(6)	0.005(3)
C(27)	0.034(4)	0.046(4)	0.164(10)	0.040(6)	−0.010(5)	0.000(3)

Table E. Hydrogen coordinates and isotropic displacement parameters ($Å^2$) for **(+)-173A**.

	x	y	z	U
H(2A)	0.2848	0.1122	−0.0316	0.038
H(3A)	0.1177	0.1132	0.0449	0.032
H(5A)	0.0324	−0.0179	−0.0455	0.038
H(6A)	−0.0222	−0.1768	−0.0757	0.051
H(7A)	0.2443	−0.2887	−0.0711	0.047
H(8A)	0.5638	−0.2429	−0.0407	0.054
H(9A)	0.6142	−0.0835	−0.0102	0.045
H(11A)	0.5737	0.0234	0.1058	0.062
H(12A)	0.5900	−0.1041	0.1648	0.088
H(13A)	0.2983	−0.1940	0.1825	0.083
H(14A)	−0.0079	−0.1627	0.1387	0.088
H(15A)	−0.0229	−0.0331	0.0805	0.047
H(16A)	0.4455	0.2042	0.1376	0.032
H(17A)	0.3491	0.3629	0.0668	0.038
H(17B)	0.4101	0.3758	0.1286	0.038
H(18A)	0.0670	0.2616	0.0881	0.034
H(19A)	0.2714	0.3797	0.2237	0.052
H(19B)	0.3587	0.2716	0.2296	0.052
H(19C)	0.1735	0.3072	0.2650	0.052
H(20A)	−0.1452	0.4131	0.1782	0.079
H(20B)	−0.2492	0.3382	0.2173	0.079
H(20C)	−0.2770	0.3239	0.1567	0.079
H(21A)	−0.1202	0.1192	0.1659	0.058
H(21B)	0.1013	0.0982	0.1890	0.058
H(23A)	0.1413	0.1294	0.2810	0.087
H(24A)	0.0598	0.0752	0.3604	0.106
H(25A)	−0.2645	0.0806	0.3761	0.083
H(26A)	−0.5265	0.0614	0.3180	0.089
H(27B)	−0.4175	0.1001	0.2230	0.097

Table F. Torsion angles [°] for **(+)-173A**.

C(16)–N(1)–C(1)–O(2)	–7.8(11)	C(3)–N(1)–C(1)–O(2)	–166.7(7)
C(16)–N(1)–C(1)–O(1)	172.8(5)	C(3)–N(1)–C(1)–O(1)	13.9(7)
C(2)–O(1)–C(1)–O(2)	–170.7(7)	C(2)–O(1)–C(1)–N(1)	8.7(7)
C(1)–O(1)–C(2)–C(4)	–151.2(5)	C(1)–O(1)–C(2)–C(3)	–25.9(6)
C(1)–N(1)–C(3)–C(10)	93.8(6)	C(16)–N(1)–C(3)–C(10)	–65.2(6)
C(1)–N(1)–C(3)–C(2)	–28.1(6)	C(16)–N(1)–C(3)–C(2)	172.9(5)
O(1)–C(2)–C(3)–N(1)	31.1(5)	C(4)–C(2)–C(3)–N(1)	152.4(5)
O(1)–C(2)–C(3)–C(10)	–88.4(6)	C(4)–C(2)–C(3)–C(10)	32.9(7)
O(1)–C(2)–C(4)–C(9)	17.1(7)	C(3)–C(2)–C(4)–C(9)	–100.4(7)
O(1)–C(2)–C(4)–C(5)	–163.8(5)	C(3)–C(2)–C(4)–C(5)	78.7(6)
C(9)–C(4)–C(5)–C(6)	–0.1(9)	C(2)–C(4)–C(5)–C(6)	–179.3(5)
C(4)–C(5)–C(6)–C(7)	0.6(9)	C(5)–C(6)–C(7)–C(8)	–1.3(10)
C(6)–C(7)–C(8)–C(9)	1.5(10)	C(5)–C(4)–C(9)–C(8)	0.3(9)
C(2)–C(4)–C(9)–C(8)	179.4(5)	C(7)–C(8)–C(9)–C(4)	–1.0(9)
N(1)–C(3)–C(10)–C(15)	146.8(5)	C(2)–C(3)–C(10)–C(15)	–102.4(6)
N(1)–C(3)–C(10)–C(11)	–31.4(7)	C(2)–C(3)–C(10)–C(11)	79.4(7)
C(15)–C(10)–C(11)–C(12)	1.4(10)	C(3)–C(10)–C(11)–C(12)	179.6(6)
C(10)–C(11)–C(12)–C(13)	–1.1(12)	C(11)–C(12)–C(13)–C(14)	1.3(12)
C(12)–C(13)–C(14)–C(15)	–1.7(11)	C(11)–C(10)–C(15)–C(14)	–1.8(9)
C(3)–C(10)–C(15)–C(14)	179.9(5)	C(13)–C(14)–C(15)–C(10)	2.0(10)
C(1)–N(1)–C(16)–C(18)	150.8(6)	C(3)–N(1)–C(16)–C(18)	–52.5(7)
C(1)–N(1)–C(16)–C(17)	79.4(7)	C(3)–N(1)–C(16)–C(17)	–123.8(6)
N(1)–C(16)–C(17)–C(18)	109.2(5)	N(1)–C(16)–C(18)–C(17)	–109.4(5)
N(1)–C(16)–C(18)–Si(1)	136.3(4)	C(17)–C(16)–C(18)–Si(1)	–114.3(5)
C(16)–C(17)–C(18)–Si(1)	109.1(5)	C(20)–Si(1)–C(18)–C(16)	171.9(4)
C(19)–Si(1)–C(18)–C(16)	50.2(5)	C(21)–Si(1)–C(18)–C(16)	–70.4(5)
C(20)–Si(1)–C(18)–C(17)	99.4(5)	C(19)–Si(1)–C(18)–C(17)	–22.3(6)
C(21)–Si(1)–C(18)–C(17)	–142.9(5)	C(20)–Si(1)–C(21)–C(22)	–63.0(7)
C(19)–Si(1)–C(21)–C(22)	58.5(7)	C(18)–Si(1)–C(21)–C(22)	178.5(5)
Si(1)–C(21)–C(22)–C(23)	–74.0(8)	Si(1)–C(21)–C(22)–C(27)	103.3(7)
C(27)–C(22)–C(23)–C(24)	6.6(14)	C(21)–C(22)–C(23)–C(24)	–176.0(10)
C(22)–C(23)–C(24)–C(25)	–12.4(17)	C(23)–C(24)–C(25)–C(26)	15.1(18)
C(24)–C(25)–C(26)–C(27)	–11.0(16)	C(23)–C(22)–C(27)–C(26)	–1.0(10)
C(21)–C(22)–C(27)–C(26)	–178.4(6)	C(25)–C(26)–C(27)–C(22)	2.4(10)



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Scheme A